Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende chlormethin-gel til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Chlormethin-gel

Kutant T-cellelymfom af typen mycosis fungoides

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	**Apotekernes indkøbspris**
CR	***Complete response***
DKK	**Danske kroner**
DRG	**Diagnose Relaterede Grupper**
KTCL	**Kutane T-cellelymfomer**
MF	**Mycosis Fungoides**
mSWAT	***Modified Severity-Weighted Assessment Tool***
PD	***Progressive Disease***
PR	***Partial Response***
PUVA	**8-methoxypsoralen + UV-A**
SAIP	**Sygehusapotekernes indkøbspriser**
SDT	***Skin Directed Therapy***
TNMB	***Tumour-, node-, metastases- and blood***

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for chlormethin ca. [redacted] pr. patient sammenlignet med PUVA. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 645.000 DKK pr. patient. Den højere inkrementelle omkostning for behandling af chlormethin er drevet af omkostningerne til lægemidlet.

Der er usikkerhed forbundet med de estimerede inkrementelle omkostninger, på grund af potentiel stor variation i forløb på tværs af patienter og muligheden for individualiseret dosering af chlormethin samt lav kvalitet af evidensen, der har ligget til grund for analysen.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af chlormethin som mulig standardbehandling vil være ca. [redacted]. DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 1,68 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af chlormethin som mulig standardbehandling på danske hospitaler til topikal behandling af kutant T-cellelymfom af typen Mycosis Fungoides (MF).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Recordati. Vi modtog den endelige ansøgning den 31. maj 2022.

3.1 Patientpopulation

MF er en type af kutane T-cellelymfomer (KTCL), som er en sjælden gruppe af non-Hodgkin lymfomer, hvor MF udgør 50-60 % af KTCL-tilfældene. Ved diagnose er medianalderen 55-60 år med overvægt af mænd. MF viser sig i form af erythematøse patches, plaques i huden og, sjældnere, tumorer i huden og er almindeligvis langsomt progredierende [1]. Patienterne er plagede af deres hudsymptomer, som har stor indflydelse på livskvaliteten. Hos nogle patienter optræder der behandlingsresistente patches eller plaques og/eller patches eller plaques i hoved-/halsregionen eller kønsdelene, som kan være særligt generende. Patienterne er særligt plagede af deres hudsymptomer, som i de tidlige stadier er i form af tørt, rødt, skællende og kløende udslæt. Forandringerne kan i starten være diskrete og ligne eksem eller psoriasis, men bliver over tid mere udtalte og fortykkede (patches og/eller plaques). Hudforandringer har stor indflydelse på patienternes livskvalitet. Hudforandringerne kan være afgrænsede til mindre dele af kroppen, men kan også være udbredt over store dele af kroppen. Hudforandringerne er ikke spontant remitterende, men kan bedres med behandling.

I tidlige stadier af MF (IA-IIA), når sygdommens udbredelse er begrænset til huden, anvendes topikal behandling i form af f.eks. kortikosteroider i kombination med ultraviolet lysbehandling (smalspektret UVB eller 8-methoxypsoralen + UV-A (PUVA)) eller penslinger med kvælstof-sennepsgas. Målet med de topikale behandlinger er at reducere udbredelsen af patches/plaques og dermed forbedre patientens livskvalitet. Herudover kan effektiv topikal behandling udskyde tiden til, at patienten må overgå til systemisk behandling, som er forbundet med flere bivirkninger.

I Danmark lever ca. 250-300 patienter med behandlingskrævende MF-KTCL (lokal såvel som systemisk behandling). Fagudvalget vurderer, at ca. 10-15 % (n=30) af disse patienter vil blive behandlet med chlormethin-gel, og at antallet af patienter vil være konstant over tid.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af chlormethin på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne patienter med tidlige stadier af MF (I-IIA), som har modtaget mindst én tidligere topikal behandling?

Klinisk spørgsmål 2:

Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne MF-patienter (uafhængigt af stadie) med særligt behandlingsresistente patches eller plaques og/eller patches eller plaques i hoved-/halsregionen og på kønsdelene, og som har modtaget mindst én tidligere topikal behandling?

Medicinrådet vurderer, at PUVA er den mest relevante komparator, da det er det mest hyppigt anvendte behandlingsalternativ, og derfor præsenteres kun resultater for PUVA i hovedanalysen, men Medicinrådet vælger at foretage en følsomhedsanalyse, hvor UVB anvendes som komparator.

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for chlormethin sammenlignet med PUVA. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske sammenligning af chlormethin med PUVA er foretaget på baggrund af adskillige studier. Effekten af chlormethin er baseret på det observant-blindede fase II-studie *Study 201* [2] samt kohortestudiet foretaget af Kim et al. [3]. I *Study 201* blev patienter randomiseret til behandling med chlormethin enten som gel eller salve som administrationsform. Effektforskelle mellem de to administrationsformer blev evalueret ved forskelle i responsrater ved det primære effektmål CAILS og det sekundære effektmål mSWAT. Kohortestudiet af Kim et al. var en retrospektiv analyse, der undersøgte samlet- og progressionsfri overlevelse samt risiko for relaps hos MF-

patienter, der blev behandlet med topikale penslinger af kvælstof-sennepsgas som initial behandling.

Effekt af PUVA er i ansøgers hovedanalyse baseret på registerstudiet *PROCLIPI* [4], fase III-studiet *EORTC* [5] og en meta-analyse foretaget af Phan et al. [6], og dermed ikke svarende til de studier, der anvendes til at estimere den kliniske effekt i vurderingsrapporten. *PROCLIPI*-studiet er et internationalt registerstudie, hvor der samles relevant data for MF-patienter i tidlige stadier [4]. Her har ansøger benyttet data fra engelske patienter, under antagelse om at data for denne population kan overføres til danske MF-patienter. *EORTC*-studiet er et randomiseret fase III-studie, der sammenligner effekt hos stadie IB og stadie IIA MF-patienter målt ved overordnet klinisk respons af behandling med PUVA i kombination med bexarotene versus behandling med PUVA alene. Meta-analysen foretaget af Phan et al. sammenligner effekt af PUVA med smalspektret UVB for MF-patienter i tidlige stadier via en systematisk litteratursøgning og definerede eksklusionskriterier. Effekt er her opgjort ved forskelle i overordnet klinisk respons og antal af patienter, der oplever et tilbagefald af sygdom.

Ansøgers omkostningsanalyse indeholder ikke en besvarelse af klinisk spørgsmål 2 fra Medicinrådets protokol, da det ikke er lykkedes ansøger at finde passende data for patientpopulationen defineret i dette spørgsmål. Ligeledes har det ikke været muligt for ansøger at finde tilstrækkeligt data til at foretage en analyse, der viser værdien af chlormethin sammenlignet med topikale kortikosteroider, hvorfor denne komparator ikke indgår i omkostningsanalysen.

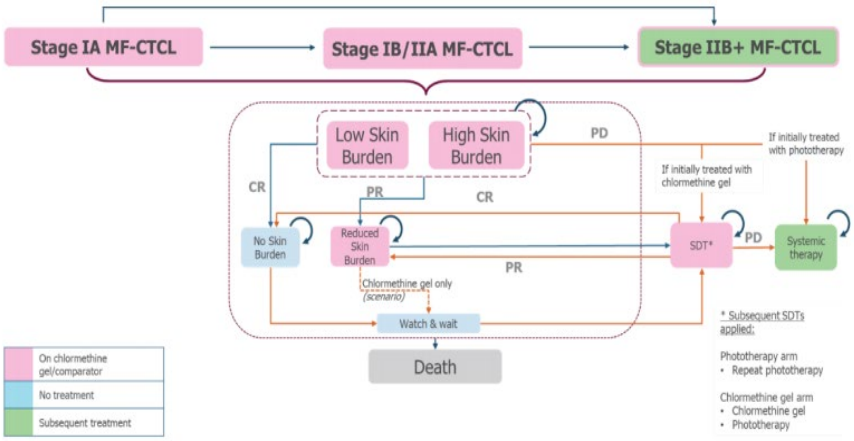
4.1.1 Modelbeskrivelse

Ansøger har indsendt en Markov-model til at estimere de inkrementelle omkostninger forbundet med behandlingen med chlormethin.

Modellen består af en række sygdomsstadier, som patienten kan befinde sig i på et givet tidspunkt i løbet af modellens tidshorisont. Patientens bevægelse mellem disse sygdomsstadier bestemmes af transitionssandsynligheder. Hvert sygdomsstadie er forbundet med en omkostning pr. cyklus, der baserer sig på den behandling, patienten modtager i det pågældende stadie. Forskel i omkostninger mellem chlormethin og PUVA indtræder da via transitionssandsynlighederne, som varierer, betinget af type af behandling, patienten modtager. Transitionssandsynlighederne benyttet i ansøgers model er baseret på studierne beskrevet i afsnit 4.1.

Nedenfor gives en beskrivelse af de mulige sygdomsstadier i modellen samt en grafisk illustration i Figur 1.

Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen. Pilene beskriver mulige transitioner for et givet stadie. Farven på stadierne indikerer type af behandling, patienten modtager i stadiet, mens farven af pilene ikke har nogen betydning.



I ansøgers model er *tumour-, node-, metastases- and blood*-stadier (*TNMB*-stadier), der karakteriserer progression af lymfomet, grupperet i de tre overordnede stadier IA, IB/IIA og IIB+ (sidstnævnte indeholder altså *TNMB*- stadiet IIB og alle stadier derover). Stadiet patienten befinder sig i, karakteriserer patientens risiko for død, hvor risiko for progression af lymfomet samt overlevelse er identiske for patienter i behandling med chlormethin og PUVA.

For hvert af de overordnede stadier i modellen kan patienten bevæge sig i en række understadier, der er karakteriseret ved procentandel af huden, der er involveret (BSA) og reduktion, der opnås i mSWAT-score. Når patienterne indtræder i modellen og starter behandling med chlormethin eller PUVA, er de enten i stadiet low skin burden (BSA < 10 %) eller high skin burden (10 % < BSA < 80 %). Patienterne kan blive i dette initiale stadie, såfremt deres mSWAT-værdi reduceres med mindre end 50 % fra deres initiale værdi ved indtrædelse i modellen, eller den ikke stiger med mere end 25 % (herfra benævnes dette udfald *stabile disease* (*SD*)). Hvis der derimod opnås en større procentuel reduktion i mSWAT relativt til initial værdi, klassificeres det som et respons, og patienten bevæger sig til et nyt stadie. Omfanget af respons, der opnås ved initial behandling, bestemmer hvilket stadie patienten bevæger sig til. Ved *complete response* (*CR*) opnår patienten en mSWAT-score på 0 og bevæger sig til stadiet *no skin burden*, hvor behandlingen stoppes. Ved *partial response* (*PR*) opnår patienten en mSWAT reduktion > 50 % og bevæger sig til stadiet *reduced skin burden*, hvor der fortsættes med behandling.

Såfremt mSWAT stiger mere end 25 % fra baseline, da defineres det i modellen som *progressive disease* (*PD*), og patienten bevæger til en ny behandlingslinje ved en transition fra stadiet *low/high skin burden* til enten *skin directed therapy (SDT)* eller *systemic therapy*. Hvilket stadie patienten bevæger sig til, og dermed hvilken type af ny behandlingslinje der anvendes, afhænger af, hvilken behandling patienten har modtaget initialt. Såfremt patienten initialt blev behandlet med chlormethin, da bevæger patienten

sig til stadiet *skin directed therapy* (*SDT*). *SDT*-stadiet er karakteriseret ved, at alle patienter i dette stadie har modtaget minimum én topikal behandling tidligere i modellen, altså enten chlormethin eller PUVA. I dette stadie fortsættes der med den samme eller en ny topikal behandling. I situationen, hvor patienten oplever *PD* og har modtaget PUVA som initial behandling, vil patienten derimod bevæge sig fra stadiet *low/high skin burden* til stadiet *systemic therapy*. Det antages, at patienten forbliver i systemisk terapi resten af sin levetid, når dette stadie nås i modellen. I *SDT* kan patienten, ligesom i det initiale stadie, opnå respons og bevæge sig til *reduced/no skin burden*. Ligeledes kan patienten også opnå *SD* og forblive i *SDT*. Hvis patienten derimod oplever *PD*, da bevæger patienten sig ligeledes til *systemic therapy*.

Patienter i stadierne *reduced-* og *no skin burden* kan blive i disse stadier gennem deres levetid i modellen men har i hver cyklus en risiko for relaps. Såfremt en patient oplever et tilbagefald efter *PR*, bevæger de sig til *SDT*. Ligesom ved initial behandling kan patienten opnå *SD* og blive i dette stadie men kan ligeledes opnå *PR* eller *CR* og bevæge sig tilbage til hhv. *reduced skin burden* og *no skin burden*. Denne transition kan potentielt gentage sig flere gange i patientens levetid i modellen. Hvis *PD* derimod indtræffer i *SDT*-stadiet, bevæger patienten sig til *systemic therapy.* Forløbet af stadier, en patient kan bevæge sig i ved tilbagefald efter *CR,* er tilsvarende til tilbagefald efter *PR* med én undtagelse – når tilbagefaldet indtræffer, bevæger patienten sig fra *no skin burden* til stadiet *watch and wait* inden overgangen til *SDT. Watch and wait* er karakteriseret ved, at alle patienter befinder sig i otte måneder i dette stadie, hvor der ikke modtages nogen behandling. Efter de otte måneder bevæger patienterne sig automatisk til *SDT*. Inklusion af dette stadie er baseret på et argument om, at patienter, der har opnået CR, ikke vil starte i behandling med det samme efter tilbagefald.

Modellen har en cykluslængde på 1 måned, hvilket ansøger argumenterer er passende, da opfølgning i *Study 201* blev foretaget månedligt. Ansøger anvender desuden *half-cycle correction*.

Medicinrådets vurdering af ansøgers modelantagelser

Der er store usikkerheder i modellen vedr. især effekten og responsvarigheden. Fagudvalget vurderer, at effekten mellem chlormethin og PUVA er ligeværdig i forhold til at inducere et respons hos patienten. Dette er fagudvalgets vurdering i vurderingsrapporten og er baseret på det fremsendte data og fagudvalgets erfaring med pensling med kvælstof-sennepsgas, der indeholder samme virkestof som chlormethin, samt deres erfaring med PUVA-behandling. Samtidig vurderer fagudvalget, at der kan være en mulighed for at opretholde respons med chlormethin i en længere periode sammenlignet med PUVA, når patienten først har nået en respons. Som følge deraf ændrer Medicinrådet transitionssandsynlighederne for initial respons ved behandling med PUVA, således at disse er identiske med sandsynlighederne for chlormethin. Sandsynlighederne for relaps bevares fra ansøgers analyse, således at responsvarigheden af PUVA fortsat er kortere end for chlormethin i Medicinrådets anvendte model. Disse ændringer forventes at have stor betydning for analysens resultat. Transitionssandsynlighederne er præsenteret i bilaget.

Som følge af de betydelige usikkerheder omkring transitionssandsynlighederne præsenterer Medicinrådet også en følsomhedsanalyse, hvor transitionssandsynligheder for PUVA-behandling og chlormethin sættes lig hinanden på tværs af alle stadier (altså både initial respons og risiko for relaps). Der præsenteres også en følsomhedsanalyse, hvor transitionssandsynlighederne for PUVA tager udgangspunkt i ansøgers indsendte hovedanalyse.

Medicinrådet accepterer ansøgers valg af modelstruktur. Der præsenteres dog en følsomhedsanalyse, hvor patienter, der progredierer på initial behandling med chlormethin, overgår direkte til stadiet *systemic therapy* på samme vis som patienter i behandling med PUVA. Dette gøres for at belyse betydningen for resultatet af forskellen i modelstruktur.

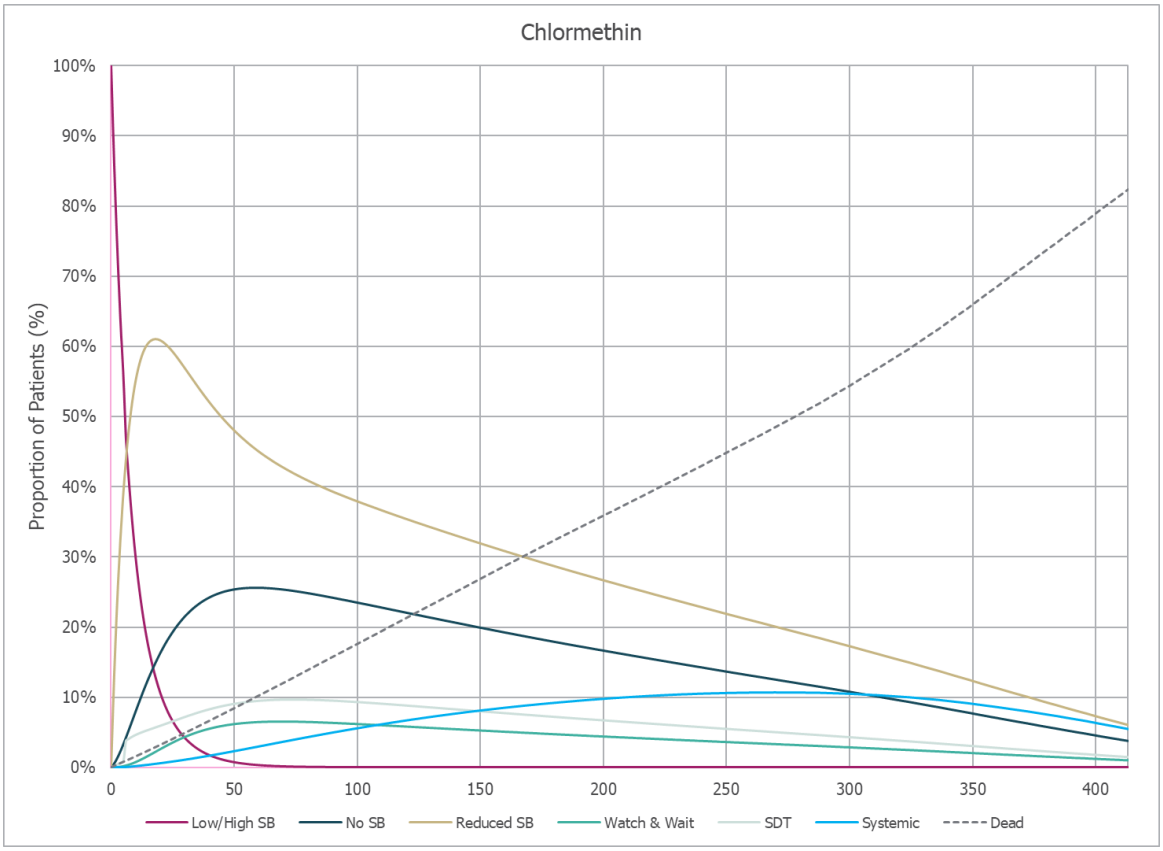
Endelig er det fagudvalgets vurdering, at otte måneder er for længe, fra en patient begynder at relapse til, at han eller hun starter i ny behandling. Baseret på deres vurdering er to måneder mere realistisk, hvorfor tiden i *watch and wait*-stadiet vurderes overestimeret. Det accepteres dog af Medicinrådet, da det vurderes at have lille betydning for det det endelige resultat. Se bilag for de eksakte transitionssandsynligheder anvendt i hovedanalysen.

Med antagelse om transitionssandsynligheder som beskrevet ovenfor, fremgår patienternes forløb i modellen for behandling med chlormethin og PUVA i hhv. Figur 2 og Figur 3. Gennemsnitlig tid tilbragt i modellens stadier fremgår af Tabel 3.

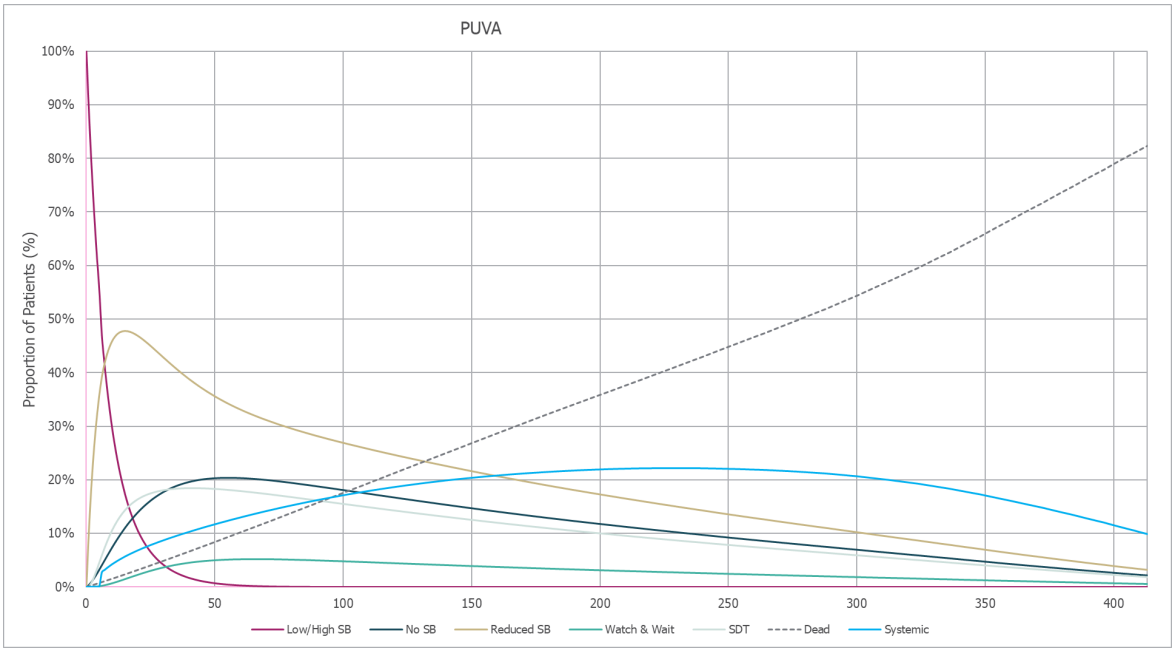
Tabel 1. Gennemsnitlig tid tilbragt i modellens respektive sygdomsstadier for chlormethin og PUVA (måneder)

	Low/high skin burden	Reduced skin burden	No skin burden	Watch and wait	SDT	Systemic therapy
Puva	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chlormethin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figur 2. Fordeling af patienter i stadier i løbet af modellen ved behandling med chlormethin. Den vandrette akse beskriver antallet af cyklusser i modellen, mens den lodrette akse beskriver procentandelen af patienter, der befinder sig i et givet stadie efter et givent antal cyklusser i modellen.



Figur 3. Fordeling af patienter i stadier i løbet af modellen ved behandling med PUVA. Den vandrette akse beskriver antallet af cyklusser i modellen, mens den lodrette akse beskriver procentandelen af patienter, der befinder sig i et givet stadie efter et givent antal cyklusser i modellen.



Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser. Dog ændres transitionssandsynlighederne for behandling med PUVA således, at de bliver identiske med transitionssandsynlighederne associeret med chlormethin behandlingen. Der udføres følsomhedsanalyser for at belyse usikkerheden ved især transitionssandsynligheder for PUVA.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metode har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en livslang tidshorisont med 44,3 år, da ansøger argumenterer for, at sygdommen er langsomt progredierende i de tidlige stadier.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år. Omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 2,5 % pr. år

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont, da MF er langsomt progredierende i de tidlige stadier set i forhold til de sene stadier af sygdommen. En livslang tidshorisont vil derfor være hensigtsmæssig til at beskrive alle relevante forskelle

i behandlingsomkostninger mellem chlormethin og PUVA. Den mediane overlevelse i modellen er 23 år.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af chlormethin sammenlignet med PUVA. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* [7], estimeret lægemiddelomkostninger på baggrund af Apotekernes indkøbspris (AIP).

Lægemiddelomkostninger inkluderet i ansøgers analyse inkluderer omkostninger til chlormethin, initial systemisk behandling og targeteret systemisk behandling i avancerede stadier. Omkostninger for PUVA-behandling er beskrevet i sektion 4.2.2.

Chlormethin
Dosis af chlormethin anvendt i ansøgers analyse er hentet i det respektive produktresumé (SPC), hvilket er angivet som et tyndt lag på de afficerede områder. Ansøger antager, at der gives en daglig dosis af 2,21 gram chlormethin gel 0,02 %, hvilket er baseret på den gennemsnitlige dosis for patienter med mellem 0-80 % afficeret BSA. I hovedanalysen medførte dette et årligt forbrug på 13,45 tuber. I ansøgers hovedanalyse er den gennemsnitlige behandlingslængde 9,18 år.

Initial systemisk behandling
Disse omkostninger er associeret med stadiet *systemic therapy* beskrevet i 4.1.1. I dette stadie antages det, at patienter modtager behandling med interferon-α og bexarotene. For interferon-α-behandling har ansøger antaget, at patienter modtager 1,5 mikrogram pr. kg ugentligt. Dosering af bexarotene er baseret på SPC, således at patienter modtager 600 mg dagligt.

Targeteret systemisk behandling:
I TNMB-stadiet IIB+ antages det, at patienter modtager behandling med interferon-α og bexarotene men yderligere også behandles med methotrexat, gemcitabin og brentuximab vedotin.

Methotrexat: 23,44 mg peroralt ugentligt, jf. *British National Formulary* [8]

Gemcitabin: 1,0-1,250 mg pr. m^2 ugentligt i 7 uger, efterfulgt af 1 uges pause

Brentuximab: 1,8 mg pr. kg hver 3. uge

Ansøger anvender en gennemsnitlig BSA på 1,91 m2 og en gennemsnitlig vægt på 79,96 kg.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 5. Jf. ændringerne af transitionssandsynligheder beskrevet i afsnit 4.1.1 bliver tid i behandling på chlormethin 9,64 år i Medicinrådets hovedanalyse. Ud fra deres nuværende erfaring med lægemidlet vurderer fagudvalget, at en daglig dosis på 2,21 gram er overestimeret, og vurderer det mere passende at anvende en daglig dosis på maks. 1,11 gram, hvor en daglig dosis på 2,21 gram anvendes i en følsomhedsanalyse for at undersøge dets indvirkning på resultatet.

Baseret på fagudvalgets vurdering ændres også de lægemidler, der anvendes, når patienterne overgår til systemisk terapi. For patienter i behandling med PUVA vurderes det, at 75 % af patienterne vil blive behandlet med interferon-alfa, når de overgår til systemisk terapi, mens de resterende vil behandles med methotrexat. For patienter i behandling med chlormethin vurderes det, at 40 % behandles med hhv. methotrexat og acitretin, mens 10 % behandles med hhv. bexaroten og interferon-alfa. Derudover vurderes det, at 50 % af patienterne vil fortsætte med chlormethin i tillæg til den systemiske behandling. For at undersøge sidstnævntes indvirkning på resultatet udarbejdes en følsomhedsanalyse, hvor der ikke anvendes chlormethin under den systemiske terapi.

Yderligere vurderer fagudvalget, at en lille andel af patienter, der behandles med PUVA, ca. 5 pct. af patienterne, vil modtage maksimalt seks behandlinger med brentuximab, når det overgår til systemisk terapi. Grundet modellens opbygning, hvor lægemiddelomkostninger tillægges pr. cyklus, har det ikke været muligt at inkorporere denne omkostning. Det vurderes at have minimal betydning for resultatet, som følge af det lille antal patienter det drejer sig om.

Omkostninger til targeteret systemisk behandling inkluderes ikke i Medicinrådets hovedanalyse. Dette er beskrevet yderligere i afsnit 4.2.3.

Tabel 2. Anvendte lægemiddelpriser, SAIP, (August 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Chlormethin	160 mikrogram/g	60 g	[redacted]	Amgros
Interferon- alfa	180 mikrogram	4 stk.	[redacted]	Amgros
Bexarotene	75 mg	100 stk.	[redacted]	Amgros
Methotrexat	50 mg/ml	0,5 ml	[redacted]	Amgros
Acitretin	25 mg	100 stk.	[redacted]	Amgros

Medicinrådet ændrer ansøgers antagelser om dosering af chlormethin og de lægemidler, der anvendes i forbindelse med systemisk terapi.

4.2.2 Hospitalsomkostninger

I relation til hospitalsomkostninger har ansøger inkluderet omkostninger i forbindelse med administrations-, monitorerings- og bivirkningsomkostninger samt omkostninger, der indtræffer som følge af patientens død (terminale omkostninger).

Administrationsomkostninger

Administrationsomkostninger omfatter i ansøgers model de estimerede udgifter i relation til PUVA-behandling samt administrationsomkostninger i forbindelse med efterfølgende systemisk behandling. Der er i modellen ikke antaget nogen omkostninger i forbindelse med administration af chlormethin. Der er heller ikke antaget nogen administrationsomkostninger i forbindelse med lægemidlerne, der anvendes som systemisk terapi, da det vurderes, at patienterne selv står for administration af lægemidlet.

For PUVA-behandling benytter ansøger DRG-takster til at estimere omkostningen af behandlingen. Det antages her, at patienten i én behandlingskur modtager behandling to gange ugentligt i otte uger [9,10]. Behandlingen gives på én af de få afdelinger, der tilbyder behandlingen i Danmark. Ansøger har, baseret på rådgivning fra Medicinrådet inden den endelige ansøgning blev indsendt, inkorporeret i deres model, at patienter maksimalt kan modtage 200 PUVA-behandlinger i deres levetid. Årsagen til dette maksimum beror på en risiko for at udvikle hudkræft senere, såfremt antal PUVA-behandlinger overstiger dette antal.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet vurderer ikke, at ansøgers metode til at estimere omkostninger til PUVA afspejler klinisk praksis. Det skyldes, at det i modellen antages, at patienter modtager behandlingskure kontinuerligt, så længe de er i behandling med PUVA, hvor der i praksis vil være en given tidsperiode uden behandling mellem hver kur. Længden af tidsperioden vil variere mellem patienter, som følge af sygdomsbyrde og tid til relaps, men fagudvalget vurderer, at man maksimalt vil give to behandlingskure årligt. Som følge deraf justerer Medicinrådet omkostningerne til PUVA-behandling, således at omkostningerne pr. cyklus svarer til 2 behandlingskure årligt. Derudover rettes antal administrationer i en behandlingskur til 3 gange ugentligt i 10 uger.

Medicinrådet vælger også at præsentere en følsomhedsanalyse, hvor patienten maksimalt kan modtage 60 PUVA-behandlinger, da dette kan være tilfældet for en række patienter, der er særligt eksponeret for hudkræft som følge af alder og erhverv.

Anvendte enhedsomkostninger kan ses i Tabel 6.

Tabel 3. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Frekvens pr. cyklus (30. dage)	Kode	Kilde
PUVA-behandling	3.203	13,04	17MA98 (1-dagsgruppe, pat. Mindst 7 år)	[DRG-2021]

Medicinrådet ændrer omkostning pr. cyklus i forbindelse med PUVA-behandling og antal administrationer i en PUVA-behandlingskur. Der præsenteres en følsomhedsanalyse, hvor maksimale antal PUVA-behandlinger ændres.

Monitoreringsomkostning

På tværs af alle stadier beskrevet i afsnit 4.1.1 er det antaget, at patienterne går til kontrol hver tredje måned – uanset hvilken type af behandling, de modtager. I ansøgningen har ansøger antaget, at et kontrolbesøg er forbundet med en omkostning på 3.203 DKK baseret på DRG-takst 17MA98 (1-dagsgruppe, pat. Mindst 7 år).

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Terminale omkostninger

Ansøger inkluderer i sin ansøgning en omkostning i modellen, når patienter dør. Omkostninger forbundet med dette er estimeret ved brug af DRG-takst (17MA01) svarende til 43.901 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. terminalomkostninger

Medicinrådet vælger at fjerne omkostninger i forbindelse med død fra ansøgers model, da ansøger ikke har redegjort for, hvad denne indeholder. Da levetid i modellen er uafhængig af, hvorvidt patienten får chlormethin eller PUVA, har omfang og inklusion af denne omkostning ikke nogen indflydelse på resultatet af de inkrementelle omkostninger.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger i forbindelse med bivirkninger som følge af behandling med chlormethin. Bivirkningsfrekvenser for chlormethin blev identificeret via *Study 201*. Omkostninger forbundet med disse blev estimeret via DRG-takster. Ansøger har ikke inkluderet bivirkningsomkostninger ved PUVA, da ansøger ikke har fundet nogle informationer om bivirkningsfrekvenser associeret med denne behandling.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger men bemærker, at ekskludering af bivirkninger ved PUVA bidrager med usikkerhed til modellen. Dette vil sandsynligvis underestimere omkostningerne ved PUVA og få chlormethin til at fremstå dyrere, men vurderes at have en minimal betydning for

resultatet, da de inkrementelle omkostninger hovedsageligt er drevet af forskelle i behandlingsomkostninger. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 7.

Tabel 4. Rapporterede bivirkningsfrekvenser ved behandling med chlormethin og PUVA samt enhedsomkostninger for bivirkningerne

	Chlormethin [%]	PUVA [%]	DRG-kode	Takst
Dermatitis	[redacted]	0	17MA98	3,203 DKK
Erytem (rødligt udslæt)	[redacted]	0	17MA98	3,203 DKK
Hudirritation	[redacted]	0	17MA98	3,203 DKK

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Efterfølgende behandling

Som beskrevet i afsnit 4.2.1 og 4.2.2 har ansøger i sin analyse inkorporeret omkostninger forbundet med behandling af patienters sygdom i TMNB-stadie IIB+, hvor patienterne modtager targeteret systemisk behandling. Omkostninger forbundet med denne behandling er dog ikke influeret af, hvorvidt patienten tidligere er blevet behandlet med chlormethin eller PUVA, da progression i TNMB-stadier er uafhængig af disse.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet vælger at fjerne omkostninger forbundet med targeteret systemisk behandling i ansøgers model, siden disse ikke er influeret af, hvorvidt patienten modtager behandling med chlormethin eller PUVA, og dermed ikke har nogen betydning for de inkrementelle omkostninger.

Medicinrådet fjerner omkostninger forbundet med targeteret systemisk behandling i stadie IIB+ fra modellen i Medicinrådets hovedanalyse.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 99 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger i forbindelse med kontrolbesøg samt behandling med PUVA. For behandling med PUVA er det antaget, at en behandling tager 30 minutter på hospitalet, dertil kommer 60 minutters samlet transporttid pr. behandling. Patienttid i forbindelse med kontrolbesøg for begge behandlinger er af tilsvarende størrelse.

Der er i ansøgers analyse ikke inkorporeret, at patienter kan have længere transporttid til PUVA-behandling, som følge af at behandlingen kun udbydes få steder i Danmark. Det skyldes, at denne estimering ifølge ansøger vil være forbundet med stor usikkerhed og have lille indflydelse på resultatet.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af patientomkostninger.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført af ansøger:

- Benytter responsrater for PUVA identificeret i metanalysen af Phan et al. frem for de, der er identificeret i PROCLIPI-studiet
- Data for progressionsfri overlevelse identificeret i Wernham et al.[11] frem for Agar et al., der benyttes i hovedanalysen
- Tidshorisont ændres fra livslang til 20 år
- Dosis for *low skin burden-patienter ændres fra 2,21 g til 1,31 g.* Dosis for *high skin burden* ændres fra 2,21 g til 3,46 g
- Administration af chlormethin ændres fra dagligt til 3,44 gange pr. uge
- Behandling med PUVA ændres fra 2 gange ugentligt til 3 gange ugentligt.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyse
Medicinrådet vælger ikke at præsentere nogle af ansøgers følsomhedsanalyser men har udarbejdet en række andre følsomhedsanalyser, der i stedet præsenteres. Disse følsomhedsanalyser er præsenteret i Tabel 10.

Tabel 5. Medicinrådets Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Risiko for relaps sættes lig hinanden for PUVA og chlormethin	Risiko for relaps efter at have opnået *reduced skin burden* eller *no skin burden* ved PUVA-behandling sættes lig risikoen ved behandling med chlomethin (således at modellen antager identisk klinisk effekt mellem chlormethin og PUVA).
Forskel i induktion af respons- og relapssandsynligheder mellem chlormethin og PUVA	Anvendelse af transitionssandsynligheder fra ansøgers indsendte hovedanalyse, hvor chlormethin er mere effektiv i både at inducere et respons hos patienten samt at minimere risiko for relaps.

Følsomhedsanalyse	Beskrivelse
Patienter i behandling med chlormethin går direkte til systemisk terapi ved initialt manglende effekt af behandling	Strukturen i modellen ændres således, at patienterne går direkte til systemisk terapi i tilfælde af forværring af hudsymptomer ved initial behandling med chlormethin og ikke til stadiet *SDT,* hvor patienterne behandles med PUVA (ens modelstruktur for PUVA og chlormethin).
Dosis af chlormethin fra *Study 201* anvendes	Dosering af chlormethin ændres fra 1,105 gram dagligt til 2,21 gram dagligt.
Chlormethin ikke anvendt i kombination med systemisk terapi	Andelen, der modtager chlormethin under systemisk terapi, ændres fra 50 % til 0 %.
Reduktion i pris for PUVA	Prisen pr. PUVA-behandling reduceres med 50 %.
Stigning i pris for PUVA	Prisen pr. PUVA-behandling øges med 50 %.
Ændring af maksimalt antal PUVA-behandlinger	Maksimalt antal behandlinger med PUVA ændres fra 200 til 60.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser men har i stedet udarbejdet en række egne følsomhedsanalyser, der præsenteres.

4.4 Opsummering af basisantagelser

I Tabel 10 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	Livstid	Livstid
Diskonteringsrate	0 % år 1 3,5 % år 1-35, 2,5 % efterfølgende år	0 % år 1 3,5 % år 1-35, 2,5 % efterfølgende år
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger Terminale omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger
Dosering	Chlormethin: 2,21 gram dagligt PUVA: op til 60 behandlinger	Chlormethin: 1,105 gram dagligt Op til 200 behandlinger

Basisantagelser	Ansøger	Medicinrådet
Transitionssandsynligheder for stadier i Markov-modellen	Samlet og progressionsfri overlevelse: Agar et al. Chlormethin: Study 201, Kim et al., PROCLIPI PUVA: PROCLIPI, Whittaker et al., Phan et al.	Samlet og progressionsfri overlevelse: Agar et al. Chlormethin: Study 201, Kim et al. PROCLIPI, Fagudvalg PUVA: Study 201, Kim et al., Fagudvalg
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der er beskrevet ovenfor.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning ca. 645.000 DKK pr. patient.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 11.

Tabel 7. Resultatet af Medicinrådets hovedanalyse ved sammenligning med PUVA, DKK, diskonterede tal

	Chlormethin (DKK)	PUVA (DKK)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger til chlormethin	[redacted]	[redacted]	[redacted]
Lægemiddelomkostninger til Systemisk Behandling	[redacted]	[redacted]	[redacted]
Administrationsomkostninger til PUVA	0	364.592	-364.592
Monitoreringsomkostninger	179.386	179.386	0
Bivirkningsomkostninger	6.526	0	6.526
Patientomkostninger	29.594	51.671	-22.077

	Chlormethin (DKK)	PUVA (DKK)	Inkrementelle omkostninger (DKK)
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 12.

Tabel 8. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Risiko for relaps sættes lig hinanden for PUVA og chlormethin	[redacted]
Forskel i induktion af respons- og relapssandsynligheder mellem chlormethin og PUVA (anvendelse af ansøgers transitionssandsynligheder)	[redacted]
Patienter i behandling med chlormethin går direkte til systemisk terapi ved initialt manglende effekt af behandling	[redacted]
Dosis af chlormethin fra *Study 201* anvendes (daglig dosis ændres fra 2,21 til 1,105)	[redacted]
Chlormethin ikke anvendt i kombination med systemisk terapi	[redacted]
Pris for PUVA reduceres med 50 %	[redacted]
Pris for PUVA øges med 50 %	[redacted]
Ændring af maksimalt antal PUVA-behandlinger	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at chlormethin vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Chlormethin bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Chlormethin bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Baseret på Medicinrådets protokol har ansøger antaget, at 275 patienter er kandidater til behandling med chlormethin, og at dette antal vokser med 30 patienter årligt. Det antages dog af ansøger, at det kun er en andel af den relevante population, der vil blive behandlet med chlormethin i tilfælde af en anbefaling. Mere specifikt antages det, at 5 % af populationen vil blive behandlet med chlormethin i år 1, mens andelen vil være 18 % i år 5. Såfremt chlormethin ikke anbefales, antager ansøger, at markedsandelen vil være på 0 % i år 1-5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis chlormethin anbefales som mulig standardbehandling, og hvis ikke chlormethin anbefales. Baseret på den erfaring, der er opnået siden udarbejdelsen af Medicinrådets protokol, estimeres det, at der årligt vil være omkring 30 patienter, se Tabel 14. Patientantallet vurderes at være stabilt, da en tilsvarende andel vil påbegynde og afslutte behandling.

Tabel 9. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Chlormethin	30	30	30	30	30
PUVA	275	275	275	275	275
			Anbefales ikke		
Chlormethin	0	0	0	0	0
PUVA	275	275	275	275	275

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er 30 patienter årligt.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse. Medicinrådet estimerer, at anvendelse af chlormethin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 14.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 1,68 mio. DKK i år 5.

Tabel 10. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB: Da omkostninger fluktuerer mellem de to behandlinger over modellens tidshorisont, kan budgetkonsekvenserne udvikle sig anderledes efter år 5.

7. Diskussion

Behandling med chlormethin er i Medicinrådets hovedanalyse forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med PUVA-behandling.

Der er betydelige usikkerheder i den sundhedsøkonomiske model, særligt i relation til de anvendte transitionssandsynligheder og patienternes forløb igennem modellens mange stadier. På basis af fagudvalgets mangeårige erfaring med kvælstof-sennepsgas penslinger er det muligt at udtale sig om den kliniske effekt af chlormethin og PUVA relativt til hinanden, men der er fortsat usikkerhed om de faktiske transitionssandsynligheder som følge af den sparsomme kliniske evidens. Sidstnævnte er dog af mindre betydning, da det er den kliniske effekt af chlormethin relativt til PUVA, der er mest afgørende for de inkrementelle omkostninger. Ydermere kan et behandlingsforløb variere betragteligt mellem patienter som følge af sygdommens karakteristika og de mange behandlinger, der anvendes i dansk klinisk praksis. Dette bidrager også til usikkerheden i estimeringen af de inkrementelle omkostninger, da det forstærker kompleksiteten i at tage højde for, hvordan anvendelse af chlormethin vil påvirke brug af de nuværende standardbehandlinger.

Fra de foretagne følsomhedsanalyser findes det, at flere ændringer af antagelser har en vis indvirkning på resultatet, mens dosering af chlormethin har stor betydning for resultatet af de inkrementelle omkostninger. Medicinrådet anvender i sin hovedanalyse den dosering, som, fagudvalget vurderer, vil blive brugt på basis af deres nuværende erfaring med lægemidlet, som stemmer overens med publiceret *Real World Evidence* [12]. Anvendes doseringen fra *Study 201,* stiger de inkrementelle omkostninger med [redacted]. Usikkerheden om dosering er også af betydeligt omfang, siden graden af hudinvolvering hos patienten har indflydelse på dosering. Spørgsmålet om dosering blev også adresseret i vurderingen foretaget af *National Institute of Clinical Excellence (NICE)*. Her blev en dosis på 2,8 gram anvendt på basis af lægemidlets produktresumé, men det blev samtidig konkluderet, at denne dosis sandsynligvis var en kraftig overestimering. Denne konklusion blev draget på basis af de kliniske eksperters udtalelser om, at der var betydelig usikkerhed omkring dosering, men at det sandsynligvis ikke ville være mere end 6 tuber årligt (svarende til den anvendte dosis i Medicinrådets hovedanalyse) [13].

En tube chlormethin koster i rene lægemiddeludgifter [redacted] DKK og ved anvendelsen af maks. 6 tuber årligt vil den maximale udgift være [redacted] DKK om året. Der vil dog være en lavere samlet udgift i det, at patienterne ikke samtidig behandles med PUVA og evt. anden behandling som kan undværes i perioden, hvor chlormethin kan holde hudsymptomerne i bero.

8. Referencer

1. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017. Bd. 77, European Journal of Cancer. Elsevier Ltd; 2017. s. 57–74.

2. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, et al. Topical chemotherapy in cutaneous T-cell lymphoma: Positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol. 2013;149(1):25–32.

3. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Arch Dermatol. 2003;139(2):165–73.

4. Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, et al. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. British Journal of Dermatology. 2019;181(2):350–7.

5. Whittaker S, Ortiz P, Dummer R, Ranki A, Hasan B, Meulemans B, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: Final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056. British Journal of Dermatology. 2012;167(3):678–87.

6. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. Comparison of Narrowband UV-B with Psoralen-UV-A Phototherapy for Patients with Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019;155(3):335–41.

7. Medicinrådet. Metodevejledning for omkostningsanalyser af nye laegemidler og indikationer i hospitalssektoren.

8. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. British Journal of Dermatology. 2019;180(3):496–526.

9. PUVA lysbehandling [Internet]. Sjællands Universitetshospital i Roskilde [internet]. Tilgængelig fra: https://www.regionsjaelland.dk/sundhed/geo/roskildesygehus/Afdelinger/dermatologisk-afdeling/hudsygdomme/Lysbehandling/Sider/PUVA-lysbehandling.aspx

10. Tablet PUVA-behandling - Regionhospitalet Viborg [internet]. Tilgængelig fra: https://www.hospitalsenhedmidt.dk/patientvejledninger/medicinsk-afdeling/tablet-puva-behandling/

11. Wernham AG, Shah F, Amel-Kashipaz R, Cobbold M, Scarisbrick J. Stage i mycosis fungoides: Frequent association with a favourable prognosis but disease progression and disease-specific mortality may occur. British Journal of Dermatology. 2015;173(5):1295–7.

12. Kim EJ, Guitart J, Querfeld C, Girardi M, Musiek A, Akilov OE, et al. The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. Am J Clin Dermatol. 2021;22(3):407–14.

13. Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [internet]. 2021. Tilgængelig fra: www.nice.org.uk/guidance/ta720

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. oktober 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Transitionssandsynligheder anvendt i Medicinrådets hovedanalyse

10.1.1 Chlormethin

Tabel 11. Transitionssandsynligheder for behandling med chlormethin gældende for patienter med *low skin burden* i stadie IA og IIB+. Kilde: Study 201, Kim et al., PROCLIPI

***Low skin burden,* IA og IIB+**	**Slutstadie**					
Startstadie	Low skin burden	No skin burden	Reduced skin burden	Watch and wait	SDT	Systemic therapy
Low skin burden	[redacted]	[redacted]	[redacted]		[redacted]	
No skin burden		[redacted]		[redacted]		
Reduced skin burden		[redacted]	[redacted]		[redacted]	
Watch and wait				[redacted]	[redacted]	
SDT		[redacted]	[redacted]		[redacted]	[redacted]

Tabel 12. Transitionssandsynligheder for behandling med chlormethin gældende for patienter med *high skin burden* i stadie IB/IIA og IIB+. Kilde: Study 201, Kim et al. og PROCLIPI

***High skin burden,* IB/IIA og IIB+**	**Slutstadie**					
Startstadie	High skin burden	No skin burden	Reduced skin burden	Watch & wait	SDT	Systemic therapy
High skin burden	[redacted]	[redacted]	[redacted]		[redacted]	
No skin burden		[redacted]		[redacted]		
Reduced skin burden		[redacted]	[redacted]		[redacted]	
Watch & wait				[redacted]	[redacted]	
SDT		[redacted]	[redacted]		[redacted]	[redacted]

10.1.2 PUVA

Tabel 13. Transitionssandsynligheder for behandling med PUVA gældende for patienter med *low skin burden* i stadie IA og IIB+. Kilde: Study 201, Kim et al., PROCLIPI

***Low skin burden,* IA og IIB+**	**Slutstadie**					
Startstadie	Low skin burden	No skin burden	Reduced skin burden	Watch and wait	SDT	Systemic therapy
Low skin burden	[redacted]	[redacted]	[redacted]			[redacted]
No skin burden		[redacted]		[redacted]		
Reduced skin burden		[redacted]	[redacted]		[redacted]	
Watch and wait				[redacted]	[redacted]	
SDT		[redacted]	[redacted]		[redacted]	[redacted]

Tabel 14. Transitionssandsynligheder for behandling med chlormethin gældende for patienter med *high skin burden* i stadie IB/IIA og IIB+. Kilde: Study 201, Kim et al. og PROCLIPI

***High skin burden,* IB/IIA og IIB+**	**Slutstadie**					
Startstadie	High skin burden	No skin burden	Reduced skin burden	Watch & wait	SDT	Systemic therapy
High skin burden	[redacted]		[redacted]			[redacted]
No skin burden		[redacted]		[redacted]		
Reduced skin burden		[redacted]	[redacted]		[redacted]	
Watch & wait				[redacted]	[redacted]	
SDT			[redacted]		[redacted]	[redacted]

10.2 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 44,3 år. Er analysen udført med AIP, bliver de inkrementelle omkostninger 335.449 DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 19.

Tabel 15. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Chlormethin	**PUVA**	**Inkrementelle omkostninger**
Totale omkostninger	[redacted]	[redacted]	[redacted]

*Resultaterne i afsnittet er ansøgers estimat af de inkrementelle omkostninger pr. patient. Dog har der været mindre fejl i den indsendte ansøgning, som Medicinrådet i overensstemmelse med ansøger har rettet. Derfor stemmer resultaterne ikke overens med resultaterne præsenteret i ansøgers tekniske dokument.

10.3 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Ansøger estimerer, at anvendelse af chlormethin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 20.

Tabel 16. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

06.10.2022

MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.10.2022
Leverandør	Recordati
Lægemiddel	Ledaga (chlormethin)
Ansøgt indikation	Topikal behandling af kutant T-celle-lymfom af typen mycosis fungoides

Forhandlingsresultat

Amgros har opnået følgende pris på Ledaga (chlormethin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Ledaga (chlormethin)	160 mcg/g gel	60 g	17.800	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Årlige lægemiddelomkostninger

Tabel 2: Årlige lægemiddelomkostninger

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlige lægemiddelomkostninger SAIP pr. år (DKK)
Ledaga (chlormethin)	1,11g dagligt	60 g	[redacted]	6*	[redacted]

*Baseret på Medicinrådets vurderingsrapport

Status fra andre lande

Norge: Ikke anbefalet[1]
Sverige: Ikke sygehusforbeholdt lægemiddel. TLV har tilkendt klausuleret tilskud[2].
England: Anbefalet[3]

Konklusion

Amgros vurderer, at det ikke er muligt at opnå en bedre pris på Ledaga (chlormethin).

[1] https://nyemetoder.no/metoder/klormetin-ledaga
[2] https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2022-04-25-ledaga-ingar-i-hogkostnadsskyddet-med-begransning.html
[3] https://www.nice.org.uk/guidance/TA720/chapter/1-Recommendations

Medicinrådet

Medicinrådets vurdering vedrørende chlormethin-gel til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	28. september 2022
Dokumentnummer	151705
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Klinisk spørgsmål 1

Medicinrådet finder, at den samlede værdi af chlormethin-gel til topikal behandling af voksne patienter med kutant T-cellelymfom af typen mycosis fungoides i tidlige stadier (I-IIA), som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling, ikke kan kategoriseres. Dette gælder både i sammenligning med PUVA, UVB og kortikosteroider.

Baseret på en naiv sammenstilling af data og fagudvalgets kliniske erfaring vurderer Medicinrådet, at effekten af PUVA og chlormethin formentlig er ligeværdig i forhold til at inducere et respons, mens det forventeligt vil være muligt at opretholde et respons over længere tid med chlormethin, end hvad fagudvalget vurderer er muligt med PUVA. Dette skyldes primært, at chlormethinbehandling kan fortsættes som vedligeholdelsesbehandling eller gives som gentagne behandlinger uden øvre grænse, hvis der er god effekt.

Medicinrådet vurderer, at chlormethin-gel har en bedre sikkerhedsprofil end PUVA, hvad angår langtidsbivirkninger. Chlormethin kan medføre lokale hudreaktioner, mens PUVA har en velkendt carcinogen effekt, og behandlingen har derfor begrænsninger.

Der er ikke fremsendt data for en sammenligning med UVB og kortikosteroider.

Evidensens kvalitet vurderes at være meget lav.

Klinisk spørgsmål 2

Medicinrådet finder, at den samlede værdi af chlormethin-gel specifikt til topikal behandling til voksne patienter med kutant T-cellelymfom af typen mycosis fungoides i stadie IIB-IV eller voksne patienter (uafhængigt af stadie) med patches eller plaques i hoved-/hals regionen eller på kønsdelene, som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling, ikke kan kategoriseres. Dette gælder både i sammenligning med PUVA, UVB og kortikosteroider.

Medicinrådet vurderer, ud fra fagudvalgets kliniske erfaring, at effekten af chlormethin-gel til populationen i klinisk spørgsmål 1 med rimelighed kan forventes også at gælde til populationen i klinisk spørgsmål 2. Dette begrundes med, at behandling med chlormethin vil blive målrettet samme type af patches og plaques i alle sygdomsstadier og på alle lokalisationer, hvorfor effekten kan forventes at være ens.

Evidensens kvalitet vurderes at være meget lav.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 29. september 2022

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

CAILS:	*Composite Assessment of Index Lesion Severity*
CI:	Konfidensinterval
CR:	Komplet respons
CT:	Computertomografi
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention to treat*
KTCL:	Kutant T-cellelymfom
MF:	Mycosis fungoides
mSWAT:	Modificeret *Severity Weighted Assessment Tool*
OR:	*Odds ratio*
PD:	Progressiv sygdom
PD-1:	*Programmed cell death protein 1*
PET:	Positron emissions tomografi
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
TNMB-system:	*Tumor-, node-, metastasis-, blood-system*
UV-A:	Ultraviolet lys, type A
UV-B:	Ultraviolet lys, type B

3. Introduktion

Formålet med Medicinrådets vurdering af chlormethin til kutant T-cellelymfom af typen mycosis fungoides (MF) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Recordati Rare Diseases og Helsinn Birex Pharmaceuticals Ltd. Medicinrådet modtog ansøgningen den 12. maj 2021.

De kliniske spørgsmål er:

Klinisk spørgsmål 1: Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne patienter med tidlige stadier af MF (I-IIA), som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling?

Klinisk spørgsmål 2: Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne MF-patienter (stadie IIB-IV) eller voksne MF-patienter (uafhængigt af stadie) med patches eller plaques i hoved-/halsregionen eller på kønsdelene, som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling?

3.1 Mycosis fungoides (MF)

MF er den hyppigste form af alle kutane T-cellelymfomer (KTCL). KTCL er en heterogen gruppe af sjældne non-Hodgkin-lymfomer, hvor MF udgør omkring 50-60 %. Medianalder ved diagnose er typisk 55-60 år med overvægt af mænd. MF viser sig oftest i form af erythematøse patches, plaques i huden og, sjældnere, tumorer i huden og er almindeligvis langsomt progredierende [1].

MF inddeles efter et tumor-, node-, metastases-, blod-(TNMB) system i stadier fra I-IV efter *International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer's* reviderede kriterier [2]. Stadieinddelingen omfatter normalt blodprøver, en PET-/CT-skanning og en knoglemarvsundersøgelse. Stadierne er forklaret i Tabel 1. I de tidlige stadier er sygdommen kun lokaliseret til huden, men kan over tid progrediere til lymfeknuder og evt. andre organer.

Kun omtrent 25 % af patienterne med stadie IA eller IB, hvor der kun er hudinvolvering, oplever med tiden progression til mere avancerede sygdomsstadier.

Prognosen for MF er stadieafhængig. Stadie IA og IB har en god prognose. Hos velbehandlede patienter er der rapporteret medianoverlevelse på 35,5 år, 21,5 år og 15,8 år for henholdsvis stadie IA, IB og IIA [3]. Stadie IIB og III har en medianoverlevelse på 4-6 år, mens stadie IV har en medianoverlevelse på mindre end 4 år. Sygdommen har således et meget varierende forløb med meget forskellig restlevetid. Topikal behandling kan være relevant i alle sygdomsstadier, men påvirker ikke sygdomsprogressionen.

Tabel 1. Stadieinddeling for MF

Stadie	Beskrivelse af stadie	Udbredelse
IA	Stadie 1A betyder, at mindre end 10 % af huden er involveret.	Lymfomet er begrænset til huden (patches eller plaque).
IB	Stadie 1B betyder, at 10 % eller mere af huden er involveret.	
IIA	Stadie 2A betyder, at der er patches eller plaque på huden, og lymfeknuderne er forstørrede, men de indeholder ikke unormale lymfomceller.	
IIB	Stadie 2B betyder, at der er en eller flere forhøjede tumorer i huden. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.	
IIIA	Stadie 3A betyder, at der er få eller ingen lymfomceller i blodbanen (erythrodermisk mycosis fungoides).	80 % eller mere af huden er involveret med erythrodermi (diffus rødme, fortykkelse og eventuelt sprækker i huden), hævelse, kløe og undertiden smerte. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.
IIIB	Stadie 3B betyder, at et moderat antal lymfomceller findes i blodbanen.	
IVA	Stadie 4A betyder, at der er talrige unormale lymfomceller i blodbanen (Sézarys syndrom), eller lymfeknuderne indeholder lymfomceller. Der er lymfom i huden i form af patches, plaques og/eller erythrodermi.	
IVB	Stadie 4B betyder, at lymfomet er spredt til andre organer.	

3.1.1 Hudsymptomer ved MF

Patienterne er særligt plagede af deres hudsymptomer, som i de tidlige stadier er i form af tørt, rødt, skællende og kløende udslæt. Forandringerne kan i starten være diskrete og ligne eksem eller psoriasis, men bliver over tid mere udtalte og fortykkede (patches og/eller plaques). Hudforandringer har stor indflydelse på patienternes livskvalitet. Hudforandringerne kan være afgrænsede til mindre dele af kroppen, men kan også være udbredt over store dele af kroppen. Hudforandringerne er ikke spontant remitterende, men kan bedres med behandling. Hos nogle patienter optræder der behandlingsresistente patches eller plaques og/eller patches eller plaques i hoved-/halsregionen eller kønsdelene, som kan være særligt generende.

3.1.2 Patientantal

I Danmark lever ca. 250-300 patienter med behandlingskrævende MF-KTCL (lokal såvel som systemisk behandling). Fagudvalget vurderer, at ca. 10-15 % af disse patienter vil blive behandlet med chlormethin-gel, og at antallet af patienter vil være konstant over tid.

3.2 Chlormethin-gel

Chlormethin er et celledræbende (alkylerende) middel, der hæmmer hurtigt delende celler og påbegynder en proces, hvor celler ødelægger sig selv – også kaldet programmeret celledød (apoptose). Chlormethin-gel er indiceret til topikal behandling af KTCL af typen MF og kan dermed anvendes som topikal behandling på tværs af sygdomsstadier. Det blev godkendt af EMA den 3. marts 2017 og har status som et lægemiddel til sjældne sygdomme (*orphan medicinal product*)..

Ligesom andre topikale behandlinger er chlormethin-gel ikke en kurativ behandling for MF og behandlingen påvirker ikke overlevelsen og heller ikke spredning af sygdommen til andre dele af kroppen (progression i sygdomsstadier). Chlormethin-gel forventes anvendt med det formål at holde hudsymptomerne under kontrol. Dette er vigtigt, da lindring af hudsymptomer kan forbedre patienternes livskvalitet. Hvis hudsymptomerne ikke kan kontrolleres, tilbydes patienterne systemisk terapi, selvom sygdommen ikke har spredt sig systemisk. At holde hudsygdommen under kontrol er derfor vigtigt for at udskyde tiden til den systemiske behandling.

Chlormethin kendes også under navnene mechlorethamin og kvælstof-sennepsgas. EMA har accepteret, at chlormethin har status af ”well-established therapy”, bl.a. fordi det står anført i tekstbøger og i diverse internationale behandlingsvejledninger, som en mulig behandling. EMA har derfor også accepteret, at ansøger sammenligner to formuleringer af den aktive substans (chlormethin) i et non-inferiority design. Der er anvendt forkortet ansøgning hos EMA iht. Article 10(3) of Directive 2001/83/EC, som gælder for hybride lægemidler, altså hvor man ikke kan nøjes med de farmakokinetiske undersøgelser, som bruges til vurdering af generika.

Chlormethin markedsføres nu som en gel under handelsnavnet Ledaga. Gelen på 60 g indeholder 0,02 % chlormethin svarende til 160 µg/g. Gelen påføres i et tyndt lag på de afficerede hudområder én gang dagligt. Behandlingen forventes at blive initieret med en lavere administrationsfrekvens, f.eks. tre gange ugentligt, hvorefter dosis kan optitreres til én gang dagligt ved utilstrækkelig effekt. Når der opnås et tilfredsstillende respons, vil dosis blive forsøgt reduceret ved gradvist at øge administrationsintervallerne til en vedligeholdelsesdosis på f.eks. én gang ugentligt eller hver anden uge. Det kan blive nødvendigt løbende at justere administrationsfrekvens afhængigt af tolerabilitet.

Ved alvorlige behandlingsrelaterede hudreaktioner på det behandlede område afbrydes behandlingsforløbet. Behandling genoptages ved bedring af symptomer med en lavere administrationsfrekvens f.eks. hver 3. dag.

Behandlingsvarigheden vil være individuel, og behandlingen fortsættes, så længe der er et tilfredsstillende respons, og behandlingen er veltolereret. Behandlingen bør pauseres ved komplet respons og ingen hudsymptomer. Fagudvalgets erfaring med chlormethin-gel er, at patienterne bruger maks. 6 tuber om året, svarende til en hudaffektion på maks. 30%. Behandlingen kan fortsættes sammen med anden systemisk behandling, hvis der fortsat er hudområder, som kunne have gavn af topikal behandling. Fagudvalget beskriver, at ved mere en 30 % hudaffektion vil det oftest være bedre for patienter med helkropsbehandlinger eller systemisk behandling fremfor chlormethin-gel.

3.3 Nuværende behandling

Behandlingen af kutant T-cellelymfom i Danmark varetages af de dermatologiske afdelinger i samarbejde med hæmatologiske og onkologiske afdelinger. Behandlingen følger internationale guidelines fra *European Society for Medical Oncology* og *European Organisation for Research and Treatment of Cancer* [4,5]. Der er ingen defineret standardbehandling, da behandlingen individualiseres ud fra det kutane lymfoms karakteristika, sygdommens sværhedsgrad, patientens performancestatus, komorbiditeter, tidligere behandlinger, patientens præferencer mv.

Målet med behandlingen er sygdomskontrol, forbedring af livskvalitet og symptomlindring, idet behandlingen, fraset allogen stamcelletransplantation, ikke er kurativ. Først forsøges tumorbyrden nedbragt, hvorefter sygdommen kontrolleres og følges. Behandlingsstrategien går således ud på at lindre symptomer, inducere remissioner, udskyde progression og undgå betydelig behandlingsrelateret toksicitet. Behandlingsforløbene er oftest af længere varighed (år).

3.3.1 Behandling af patches og plaques i huden

I tidlige stadier af MF (IA-IIA), når sygdommens udbredelse er begrænset til huden, anvendes topikal behandling i form af f.eks. kortikosteroider i kombination med ultraviolet lysbehandling (smalspektret UVB eller 8-methoxypsoralen + UV-A (PUVA)) eller penslinger med kvælstof-sennepsgas. Målet med de topikale behandlinger er at reducere udbredelsen af patches/plaques og dermed forbedre patientens livskvalitet. Herudover kan effektiv topikal behandling udskyde tiden til, at patienten må overgå til systemisk behandling, som er forbundet med flere bivirkninger.

Patienterne cirkulerer mellem de forskellige topikale behandlinger. Rækkefølgen kan variere fra patient til patient, fælles gælder dog, at kortikosteroider i 80-90 % af tilfældene forsøges som den initiale topikale behandling. Gentagne behandlinger med samme lægemiddel er ikke usædvanligt (dette forventes også at gælde chlormethin), og i praksis vil lysbehandling kunne følges af chlormethin eller omvendt.

Fagudvalget vurderer, at responsraterne ved topikale behandlinger er ca. 60 %. Selvom responsraterne ofte er gode ved de nuværende topikale behandlinger, har de også visse begrænsninger og gentagne behandlingssekvenser vil ofte være nødvendige. Fagudvalget vurderer, at tiden til tilbagefald efter endt PUVA-behandling er omkring 10 måneder.

Ved lysterapi udsættes hele kroppen for UV-stråling og antallet af behandlinger, især for PUVA, er begrænset af den kumulative UV-dosis (PUVA: ca. 200 behandlinger pr. livstid) grundet den øgede risiko for udvikling af kræft. Af denne årsag vil man ofte fravælge lysterapi ved begrænset hudaffektion (~10 % af huden afficeret). Ved kortikosteroidbehandling kan behandlingseffekten være aftagende over tid, og længerevarende behandling kan føre til hudatrofi (udtynding af huden), og ved behandling af større hudoverfladeareal er der risiko for systemisk påvirkning. Derfor er der også et behov for alternative topikale behandlingsmuligheder til især patienter med en begrænset hudaffektion.

Normalt fortsætter brugen af forskellige topikale behandlinger, indtil der ikke længere opleves en tilstrækkelig bedring af patientens hudsymptomer, eller de ikke længere tolereres. Topikal behandling anvendes derfor også på de afficerede hudområder i kombination med systemisk medicinsk behandling.

I Danmark har Aarhus Universitetshospital og Bispebjerg Hospital højt specialiseret funktion indenfor behandling af kutane lymfomer. Penslinger med kvælstof-sennepsgas tilbydes kun på Aarhus Universitetshospital, mens man på Sjælland har tradition for hyppigere at bruge PUVA, sammenlignet med Aarhus. Derfor kan det også forekomme, at patienter modtager behandling i en anden region, hvis dette vurderes at være den bedste løsning for patienten. I store dele af landet er der praktiske udfordringer ved at tilbyde PUVA-behandling, som skal gives 3 gange om ugen i 10 uger, da patienterne har lang transporttid til nærmeste behandlingssted. PUVA-behandling er generelt nemmere at imødekomme i hovedstadsområdet, da afstandene er mindre. Penslinger med kvælstof-sennepsgas vil ophøre inden årsskiftet, da det ikke længere kan produceres. Derfor betragtes det ikke som standardbehandling. Penslinger med sennepsgas har været brugt i årtier på Aarhus Universitetshospital, fordi en professor med interesse indenfor behandlingen satte det op. Behandlingen er besværlig at håndtere og kræver rum med undertryk og særligt sikkerhedsudstyr for personalet. I en dansk retrospektiv opgørelse over 116 MF patienter, behandlet med mustargen penslinger fra 1991 til 2009, sås en responsrate på 91,4 % og komplet respons hos 53,4 % [6]. Respons var ikke evalueret ved standardiserede målemetoder, men ved klinisk vurdering.

3.3.2 Efterfølgende behandling

De efterfølgende behandlinger beskrives, fordi fagudvalget forventer, at en effektiv topikal behandling hos nogle patienter vil kunne udskyde tiden til, at patienten har behov for systemisk terapi til behandling af hudsymptomer. Dette har betydning for patienternes livskvalitet, men kan også påvirke de samlede omkostninger for patienternes sygdomsforløb.

I senere, mere fremskredne stadier (IIB-IV) af MF, eller hvis de ovenfor beskrevne topikale behandlinger ikke længere er effektive, anvendes lavdosis elektronvolts-helkropsbestråling, lokal strålebehandling mod tumor eller systemisk medicinsk behandling i form af interferon-α, retinoider (f.eks. acitretin og bexaroten) eller lavdosis-methotrexat. De forskellige former for systemisk behandling kombineres ofte, og anvendes også ofte i kombination med topikale behandlinger og/eller ultraviolet lysbehandling. Behandlingen, der følger efter de første systemiske behandlinger

(interferon-α, retinoider, lavdosis-methotrexat), planlægges ved multidisciplinær konference med hæmatologisk afdeling, og der anvendes targeterede behandlinger, pathway-hæmmer eller kemoterapi (f.eks. højdosis-methotrexat, gemcitabin eller doxorubicin).

De targeterede behandlinger omfatter brentuximab vedotin (anti-CD30) og alemtuzumab (anti-CD52) samt pembrolizumab (PD-1-hæmmer) og mogamulizumab. Pathway-hæmmere omfatter romidepsin (histon-deacetylase-hæmmer).. Behandlingsvalget er individualiseret og guides af patientens markørudtryk. Ingen af de targeterede behandlinger/pathway-hæmmere kan betragtes som standardbehandlinger i Danmark, og romidepsin, pembrolizumab og alemtuzumab er uden for godkendt indikation (off-label). Behandlingen med disse alternativer er derfor afhængig af individuelle ansøgninger til lægemiddelkomitéerne. I dermatologien anvendes off-label-behandling i ganske stort omfang pga. manglende evidens for behandling til givne hudsygdomme.

4. Metode

Medicinrådets protokol for vurdering af chlormethin til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen. I alt 542 publikationer blev screenet baseret på titel og abstract, og 45 publikationer blev screenet baseret på fuldtekstsartikler. Ansøger har udvalgt 2 fuldtekstartikler, som indeholder data fra 2 studier. Herudover har ansøger inkluderet et multicenter, prospektivt observationsstudie fra USA. Tabel 2 indeholder en oversigt over de inkluderede studier.

Tabel 2. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population
Topical Chemotherapy in Cutaneous T-cell lymphoma. Positive results of a Randomised, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02 % Gel in Mycosis Fungoides (2013) [7]	Study 201	NCT00168064	Voksne med mycosis fungoides. Tidlig stadie (I/IIa). Tidligere topikal behandling (f.eks. topikale steroider, PUVA eller UVB).
Efficacy of Doxycycline in the Treatment of Early Stages of Mycosis Fungoides, a Randomized Controlled Trial (2019) [8]	El Sayed et al.	NCT03454945	Voksne med mycosis fungoides. Tidlig stadie (I/IIa).
Efficacy and quality of life (QoL) in patients treated with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study (Abstract, 2019 og 2020) [9,10]	PROVe	NCT02296164	Voksne med mycosis fungoides. Primært tidlig stadie (I/II) og behandlingserfarne patienter (93 % har modtaget tidl. behandling (topikal eller systemisk).

Ingen af de identificerede studier sammenligner chlormethin med de definerede komparatorer (topikale kortikosteroider, smalspektret UVB eller PUVA) i *head-to-head*-studier. Der er heller ikke identificeret studier, som muliggør en indirekte statistisk sammenligning. Ansøger har derfor anvendt en narrativ tilgang til de sammenlignende analyser.

Medicinrådets vurdering:

Medicinrådet har vurderet ansøgers litteratursøgning og udvælgelse. Litteratursøgning og udvælgelse er udført passende jf. population, intervention og komparator specificeret i protokollen, og Medicinrådet accepterer denne.

Medicinrådet har konkret diskuteret eksklusionen af en metaanalyse af Phan et al. 2019, som undersøger effekt af PUVA-behandling. Ansøger har ikke inkluderet meta-analysen, og heller ikke de studier den indeholdt i deres gennemgang, bl.a. fordi studierne ikke brugte validerede målemetoder for respons. Fagudvalget er enigt i denne betragtning. Fagudvalget vurderer, at anvendelse af ikke-validerede målemetoder giver anledning til for stor usikkerhed, og at responsraterne er overestimerede ud fra deres kliniske erfaring. Studierne bør derfor ikke indgå. Fagudvalget drøftede også andre årsager til eksklusion, nemlig at der i en del studier ikke skulle have været afprøvet mindst én forudgående behandling, som var specificeret i protokollen. Fagudvalget er enigt i ansøger eksklusioner og vurderer, at det udvalgte studie svarer overens med deres kliniske erfaring med PUVA, herunder især responsraten og evt. bivirkninger. Fagudvalget ønsker derfor ikke at inddrage anden litteratur.

Fagudvalget er enigt i, at en narrativ gennemgang er mest passende, da der er betydende forskelle i studierne.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Der er ikke identificeret studier på de relevante patientpopulationer og relevante effektmål med de to komparatorer: topikale kortikosteroider og UVB. Derfor indeholder ansøgningen kun en narrativ sammenligning mellem chlormethin og PUVA.

Gennemgang af studier
Study 201 er et enkelt-blindet fase II, multicenter, randomiseret, *non-inferiority*-studie, der sammenligner chlormethin 0,02 % gel med chlormethin 0,02 % salve. Chlormethin blev påført en gang dagligt. Patienter med sygdomsstadie IA påførte gel på alle læsioner, mens patienter i stadie IB og IIA påførte gel på hele kroppen (dog med undtagelse af området omkring øjnene og slimhinderne). Der blev inkluderet 260 patienter randomiseret 1:1 til enten gel eller salve. Behandlingsvarigheden var 12 måneder, medmindre patienterne oplevede sygdomsprogression, toksicitet eller andre forhold, som gjorde, at behandlingen måtte ophøre. Det primære effektmål var respons vurderet ved *Composite Assessment of Index Lesion Severity* (CAILS), mens de øvrige effektmål inkluderede respons baseret på *Severity Weighted Assessment Tool* (SWAT) og uønskede hændelser.

El Sayed et al. er et enkelt-center, randomiseret, kontrolleret fase III-studie. I studiet blev 36 patienter randomiseret 1:1 til enten doxycyklin 100 mg oralt to gange dagligt eller PUVA (8-methoxypsoralen 0,5 mg/kg, startdosis: 1-3 J/cm2 i henhold til Fitzpatricks hudtype), stigende hver anden session med 0,5 J/cm2 i henhold til graden af erytem baseret på lokale retningslinjer på forsøgscentret. Studiet inkluderede patienter med tidlig fase MF (IA-IIA). Behandlingsvarigheden var 3 måneder. Det primære effektmål var mSWAT, og de sekundære effektmål var bl.a. CAILS og uønskede hændelser.

PROVe er et multicenter, prospektivt observationsstudie fra USA. Det inkluderer 301 patienter med MF. De fleste patienter med tidlig fase MF (IA-IIA) men også en mindre andel med senere stadier. Det er rapporteret livskvalitetsdata på 298 patienter samt erfaringer med alternative doseringsfrekvenser.

Baselinekarakteristika fra de inkluderede studier fremgår af Tabel 3.

Tabel 3. Baselinekarakteristika

	Intervention (Chlormethin-gel-arm fra Study 201)	PROVe (Chlormethin obs. Studie)	Komparator (PUVA-arm fra El Sayed et al.)
N	130	298	18
Alder	18-64 år: 71,5 % (93) 65-74 år: 22,3 % (29) ≥ 75 år: 6,2 % (8)	Median: 62 år (21-90)	Mean: 43,3 år (SD: 10,2)
Køn (% M/K)	59,2 % / 40,8 %	60,1 % / 39,9 %	27,8 % / 72,2 %
Sygdomsvarighed (median/range)	Højst 1 år	2,9 år (0-48)	9,5 år (2-25)
MF-stadie			
IA	58,5 % (76)	41,9 % (125)	11,1 % (2)
IB	40 % (52)	26,2 % (78)	77,8 % (14)
IIA	1,5 % (2)	3,0 % (9)	11,1 % (2)
IIB - IV	-	10,1 % (30)	-
Ikke oplyst	-	18,8 % (56)	-
CAILS score (mean ± SD)	37,3 (17,5)	Ikke målt	56,5 ± 17,2
mSWAT score (median/range)	9,0 (1-104)	Ikke målt	46,0 (7-78)
Antal tidligere behandlinger (median/range)	2 (1-12)	Ikke angivet	Ikke angivet

Der er flere forskelle mellem chlormethin-gel-armen fra *study 201* og PUVA-armen fra El Sayed et al. Der indgår f.eks. en større andel af kvinder i studiet med PUVA. Dette undrer fagudvalget, da MF sædvanligvis forekommer hyppigere hos mænd. Derfor er det også tvivlsomt, om populationen i studiet er repræsentativ i forhold til en dansk population.

Hvad angår sygdomssværhedsgrad bemærker fagudvalget, at patienterne i El Sayed et al. studiet har mere fremskreden sygdom, end tilfældet er i chlormethin-armen i *Study 201*. Dette er bl.a. afspejlet i fordelingen på tværs af sygdomsstadier, hvor ca. 59 % af patienterne i *Study 201* har MF stadie IA mod ca. 11 % i El Sayed et al. Tilsvarende er andelen af patienter i stadie IB højere i El Sayed et al. sammenlignet med *Study 201* (ca. 78 % vs. 40 %). Forskellen i fordeling på tværs af sygdomsstadier er også afspejlet i CAILS

og mSWAT-scorerne mellem studierne. Sygdomsvarigheden vurderes også at være betydeligt længere i El Sayed et al. studiet sammenlignet med *Study 201*. Disse forskelle udfordrer studiernes sammenlignelighed, idet det vurderes at være til fordel for chlormethin, da det generelt må forventes at være nemmere at inducere et respons tidligt i patienternes sygdomsforløb.

Fagudvalget vil dog fremhæve, at forskellen mellem studiepopulationerne afspejler den kliniske praksis i forhold til behandlingsvalget, da der typisk vælges kortikosteroider (og forventeligt også chlormethin) i de tidligste stadier (stadie IA/IB), hvor lysbehandling oftest først finder anvendelse fra stadie IB.

5.1.3 Evidensens kvalitet

Da denne vurdering af chlormethin er baseret på en narrativ sammenligning, kan GRADE ikke anvendes til at vurdere kvaliteten af evidensen. Kvaliteten af evidensen, som danner baggrund for vurderingen, er derfor meget lav, når det er naive sammenligninger af studiearme fra forskellige studier.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Medicinrådet har vurderet *Study 201*, som er det primære studie med chlormethin samt det randomiserede studie af El Sayed et al., der udgør datagrundlaget for PUVA. Da PROVe ikke er randomiseret, er risk of bias ikke vurderet for dette studie.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.1.4 Effektestimater og kategorier

Til denne vurdering har Medicinrådet ikke foretaget en formel kategorisering af chlormethins værdi, idet en narrativ sammenligning ikke kan danne grundlag for en kategorisering, jf. Medicinrådets metoder. Effektestimaterne fra de forskellige studier er præsenteret for hvert effektmål.

Reduktion af hudsymptomer
Som beskrevet i protokollen er effektmålet reduktion af hudsymptomer kritisk for vurderingen af lægemidlets værdi for patienterne. I de tidlige stadier af sygdommen er udbredelse primært lokaliseret til hudorganet, hvor behandlingsmålet er at opnå sygdomskontrol og dermed forbedre patienternes livskvalitet. Med udgangspunkt i fagudvalgets kliniske erfaringer på tværs af behandlinger i dansk klinisk praksis vurderede fagudvalget, at responsraten i gennemsnit ligger på ca. 60 %. Derfor fastsatte fagudvalget den mindste klinisk relevante forskel til 15 %-point. Et komplet respons (CR) kræver totalt fravær af hudlæsioner (100 % reduktion). Partiel respons (PR) kræver ≥ 50 % reduktion i mSWAT-score uden nyopståede tumorer sammenlignet med baseline. CR/PR bekræftes ved gentagen vurdering efter ≥ 4 uger.

I *Study 201's* ITT-analyse (n = 130) blev respons hen over 12 måneder på mSWAT (enten CR eller PR) opnået af 61 patienter i chlormethin-gel-armen, svarende til en responsrate på 46,9 % (95% CI: 38,3; 55,5). Heraf ni patienter med komplet respons (CR), svarende til 6,9 % (2,6; 11,3) og 40,0 % (31,6; 48,4) med partiel respons (PR).

ITT-analysen anvender en konservativ opgørelse, hvor alle, der udgår af studiet af forskellige årsager, tælles som non-response. I *Study 201* opgøres også response i efficacy-evaluable (EE)-populationen (n = 90). Responsraterne på mSWAT er her 63,3 % med chlormethin-gel. I EE-analysen analyseres udelukkende patienter, som fuldfører 6 måneders behandling. EE-analyse kan føre til et for optimistisk estimat for responsraten, da ca. halvdelen af patienterne, som ophører behandling, enten oplever betydende bivirkninger eller manglende effekt. Fagudvalget vurderer, at responsraten for chlormetin-gel forventeligt vil ligge et sted mellem estimatet for ITT- og EE-analysen.

I El Sayed et al. opnåede 50 % (9/18) patienter et respons målt med mSWAT i PUVA-armen. Ingen patienter i PUVA-armen opnåede CR, og der var dermed 50 % (27 %; 73 %), der opnåede PR. Det undrer fagudvalget, at ingen af patienterne opnåede CR, da det ifølge den kliniske erfaring er muligt at inducere et komplet respons hos en andel af patienterne.

Fagudvalget vurderer, at der ikke er data, som kan vise, om det ene behandlingsvalg er mere effektivt end det andet til reduktion af hudsymptomer. Responsraterne ligger op af, hvad fagudvalget forventer ud fra deres kliniske erfaring med penslinger med kvælstof-sennepsgas og PUVA. Fagudvalget vurderer, at effekten af PUVA og chlormethin formentlig er ligeværdig i forhold til at inducere et respons vedr. reduktion af hudsymptomer.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne. Behandlingen er palliativ, og patienternes livskvalitet undervejs i behandlingen er derfor afgørende, særligt når der er tale om patienter, som lever længe med deres sygdom. Patienternes livskvalitet er tæt forbundet med deres hudsymptomer, da hudgenerne medfører betydeligt ubehag for patienterne og samtidig en øget infektionsrisiko.

Der findes ikke data for livskvalitet i hverken *Study 201* eller El Sayed et al. Ansøger har fremsendt data fra et observationelt studie med chlormethin-gel (PROVe). Resultaterne fra PROVe er opgjort hos hhv. respondere vs. non-respondere, og resultaterne viser, at et respons på behandling er forbundet med en bedre livskvalitet.

Da der ikke foreligger data for de valgte komparatorer, er der ikke grundlag for at sammenligne chlormethin med topikale kortikosteroider, smalspektret UVB eller PUVA.

Fagudvalget vurderer, at det er forventeligt, at et respons med reduktion af hudsymptomer vil være forbundet med en bedring i patienternes livskvalitet. Dette er også tilfældet ved behandling med topikale kortikosteroider, PUVA og UVB, hvor bl.a. PROCLIPI-studiet viser, at patienternes livskvalitet bedres hos patienter i CR/PR og patienter med stabil sygdom [11].

Varighed af respons
Som beskrevet i protokollen er effektmålet varighed af respons vigtigt for vurderingen af lægemidlets værdi for patienterne, da responsvarigheden er et udtryk for sygdomskontrol hos patienterne. Varighed af respons er meget varierende og vil dels

afhænge af, hvilken behandling som gives, og om der gives vedligeholdelsesbehandling, efter der er induceret et respons.

Ansøger har ikke identificeret studier med chlormethin-gel eller de valgte komparatorer, hvor opgørelsen af responsvarighed er baseret på mSWAT. *I Study 201* er der rapporteret responsvarighed baseret på CAILS, som i flere internationale retningslinjer, som mSWAT, også er et internationalt anerkendt effektmål til brug i kliniske studier. En stor andel af de patienter, som opnår et respons (baseret på CAILS), opretholder deres respons gennem hele studiets opfølgningstid på 12 måneder. Ved 12 måneder er således ca. 85 % af patienterne, som har opnået respons i chlormethin-gel-armen, fortsat i CR eller PR. Den mediane varighed af respons er ikke opnået i studiet.

Varighed af respons er ikke vurderet i studiet af El Sayed et al. Det er fagudvalgets vurdering, at tiden til relaps i praksis ligger i størrelsesordenen ca. 10 måneder og 4-8 måneder for henholdsvis PUVA og UVB. Vedligeholdelsesbehandling anvendes sjældent efter lysbehandling, da man ønsker at begrænse den kumulerede UV-dosis. Det kan dog forekomme ved behandling med UVB.

Fagudvalget vurderer, at chlormethin har en fordel i forhold til PUVA, hvad angår varighed af respons. Dette skyldes primært, at chlormethinbehandling kan fortsættes som vedligeholdelsesbehandling eller gives som gentagne behandlinger uden øvre grænse, hvis der er god effekt.

Uønskede hændelser
Uønskede hændelser har stor betydning for den enkelte patients livskvalitet og vilje til at forblive i en behandling over længere tid, derfor er uønskede hændelser et vigtigt effektmål for vurderingen af lægemidlets værdi for patienterne. Jf. protokollen har Medicinrådet ønsket at vurdere uønskede hændelser på forekomsten af grad 3-4 uønskede hændelser og alvorlige uønskede hændelser. Forekomsten af disse hændelser er generelt meget lav med de valgte komparatorer (ca. 1 %).

Hos patienter behandlet med chlormethin-gel i *Study 201* var der i alt 84,4 % (108/128) med mindst en uønsket hændelse, heraf 61,7 % (79/128), der oplevede mindst én uønsket hændelse, som blev vurderet som relateret til behandlingen. Der var ingen systemiske bivirkninger eller toksicitet. De fleste bivirkninger var hudrelaterede og bestod primært af lokal hudirritation, kløe eller erytem (rødme/udslæt) og kontaktallergi. Der var 10,9 % (14/128), som oplevelse en alvorlig uønsket hændelse, hvoraf ingen blev vurderet som værende relateret til behandlingen med chlormetin-gel. I alt 20,3 % (26/128) af patienterne i chlormetin-gel-armen stoppede behandling grundet behandlingsrelateret hudirritation. Fagudvalget er ikke bekymret for de hudrelaterede bivirkninger, som fører til behandlingsophør i studiet. De beskriver ud fra deres erfaring med penslinger med kvælstof-sennepsgas, at en hudreaktion i forbindelse med chlormethinbehandling kan være et udtryk for, at lægemidlet har en effekt, og at det i klinisk praksis ofte kan klares med dosisjustering, hvor lægemidlet fortsat har gavnlig effekt, og bivirkningerne kan tolereres af patienten. Herudover er bivirkningerne reversible og ikke-alvorlige, og det er derfor muligt at stoppe behandling uden yderligere problemer for de patienter, som fortsat har uacceptable bivirkninger.

Studiet af El Sayed et al. rapporterer ikke uønskede hændelser grad 3-4 eller alvorlige uønskede hændelser men beskriver, at de uønskede hændelser var milde og ikke ledte til behandlingsophør.

Fagudvalget beskriver, at de kortsigtede bivirkninger ved lysterapi er få tilfælde af forbrænding, hvor UV-dosis må nedtitreres. Ved PUVA gives samtidig methoxsalen (tablet), som hos nogle patienter kan give kvalme, hovedpine og svimmelhed. Patienterne skal bære øjenbeskyttelse efter tablet indtag og resten af dagen for at beskytte øjnene. En ulempe ved lysterapi, og særligt PUVA, er risikoen for alvorlige langtidsbivirkninger. Gentagne behandlinger øger risiko for andre kræftformer i huden. Det er velkendt, at særligt PUVA har en carcinogen effekt og derfor anbefales max ~200 behandlinger pr. livstid svarende til 6-7 kure af PUVA á 3 pr. uge i 10 uger. Fagudvalget beskriver, at der for nogle patienter tilstræbes at give færre end 200 behandlinger, da den carcinogene effekt forventes at hænge sammen med antallet af behandlinger. Ved yngre patienter er afvejning vedr. langtidsbivirkninger især vigtigt, da man ikke ønsker at påføre patienten en ekstra alvorlig sygdom i en tidlig alder.

5.1.5 Fagudvalgets konklusion

Den samlede værdi af chlormethin sammenlignet med PUVA, UVB og kortikosteroider til topikal behandling af voksne patienter med kutant T-cellelymfom af typen mycosis fungoides i tidlige stadier (I-IIA), som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling, kan ikke kategoriseres jf. Medicinrådets metode.

Der findes ikke data, som muliggør en sammenligning med UVB og kortikosteroider. Fagudvalget vurderer, at chlormethin samlet set ikke har dårligere effekt eller sikkerhedsprofil end PUVA.

Fagudvalget vurderer, at effekten af PUVA og chlormethin formentlig er ligeværdig i forhold til at inducere et respons (responsraten). Data fra chlormethin-studier tyder på, at det vil være muligt at opretholde et respons over længere tid med chlormethin, end hvad fagudvalget vurderer er muligt med PUVA. I *study 201* har ~85 % af patienter, der opnår respons, fortsat respons efter 12 måneder, mens fagudvalget vurderer, at gennemsnitlig responsvarighed med PUVA er 10 måneder. Dette skyldes primært, at chlormethinbehandling kan fortsættes som vedligeholdelsesbehandling eller gives som gentagne behandlinger uden øvre grænse, hvis der er god effekt.

Fagudvalget vurderer, at chlormethin-gel har en bedre sikkerhedsprofil end PUVA, hvad angår langtidsbivirkninger. Chlormethin kan medføre lokale hudreaktioner, mens PUVA har en velkendt carcinogen effekt, og behandlingen har derfor begrænsninger.

Fagudvalget vurderer, at chlormethin-gel først bør anvendes ved utilstrækkelig effekt af topikal kortikosteroid. I en del tilfælde vil det også være relevant at have gjort et forsøg med UVB og/eller PUVA, inden man forsøger med chlormethin. Fagudvalget beskriver, at anvendelsen af chlormethin-gel forventes at være forskellig fra anvendelsen af lysbehandling. Chlormethin-gel vurderes at være særlig anvendelig til behandling af patches og plaques i de tidlige sygdomsstadier og tilsvarende lokaliserede hudsymptomer i de senere sygdomsstadier, hvor ~10-30 % af kroppen er afficeret. I de

tilfælde, hvor større dele af huden er afficeret, vil lysbehandling oftest være at foretrække. Chlormethin-gel vil derfor være et værdifuldt supplement til lysterapi og de øvrige topikale behandlinger. En yderligere fordel ved chlormetin-gel er, at det kan benyttes som hjemmebehandling, hvorimod PUVA kræver fremmøde på udvalgte klinikker, hvortil der i store dele af landet er lang transporttid.

Chlormethin vil hos alle patienter kun blive anvendt til patches og plaques med mindre grad af infiltration, idet chlormethin ikke forventes at have effekt på meget infiltrerede plaques og tumorer.

Fagudvalget har i denne vurdering inddraget det fremsendte data samt deres egen erfaring med PUVA og pensling med kvælstof-sennepsgas, som har samme indholdsstof som chlormethin-gel.

5.2 Klinisk spørgsmål 2

Der er ikke er fremsendt data for disse patienter. Derfor har Medicinrådet ikke mulighed for at foretage en kategorisering af chlormethins værdi.

Den samlede værdi af chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA specifikt til voksne patienter med kutant T-cellelymfom af typen mycosis fungoides i stadie IIB-IV eller voksne patienter (uafhængigt af stadie) med patches eller plaques i hoved-/hals regionen eller på kønsdelene, som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling, kan ikke kategoriseres.

Fagudvalget vurderer, at effekten, som ses ved behandling med chlormethin på patches og plaques i populationen i klinisk spørgsmål 1, med rimelighed kan forventes også at gælde til populationen i klinisk spørgsmål 2.

Dette begrundes med:

- Fagudvalgets erfaring med brugen af kvælstofs-sennepsgas-penslinger, som viser, at effekten er ensartet på tværs af sygdomsstadier og lokalisation af patches og plaques.
- I de mere fremskredne stadier vil behandling med chlormethin blive målrettet samme type af patches og plaques (patches og plaques uden væsentlig fortykkelse) som i de tidligere sygdomsstadier, hvorfor effekten kan forventes at være ens.

Denne vurdering af chlormethins anvendelighed på tværs af sygdomsstadier er i overensstemmelse med EMAs vurdering af indikationen for lægemidlet, som gælder alle lokalisationer og sygdomsstadier.

Fagudvalget beskriver, at patientpopulationen i spørgsmål 2 har et udækket behov for yderligere behandlingsalternativer. I de senere sygdomsstadier har patienterne ofte været igennem flere behandlinger og har derfor begrænsede muligheder tilbage. Herudover er patienterne oftest mere syge af deres grundlæggende sygdom og har derfor yderligere gavn af muligheden for hjemmebehandling til behandling af hudsymptomerne.

6. Andre overvejelser

6.1 Behandlingsvarighed og dosering

Fagudvalget efterspurgte i protokollen behandlingsvarighed med chlormethin-gel. Ansøger beskriver, at der ikke er nogen specifik behandlingsvarighed for behandling med chlormetin-gel. Behandlingen kan fortsætte, indtil patienten oplever sygdomsprogression, toksicitet, sygdom eller anden årsag, som må lede til behandlingsophør. Herudover er det forventet, at behandlingen seponeres/pauseres ved komplet respons. Ansøger opgør gennemsnitlig behandlingsvarighed ud fra *Study 201,* som har en varighed på 12 måneder. Inden for denne tidsperiode er gennemsnittet 39,3 ugers behandling. 63,3 % af patienterne var fortsat i behandling > 48 uger. Det må derfor forventes, at den gennemsnitlige behandlingsvarighed over et helt sygdomsforløb er længere. Fagudvalget beskriver, at behandling med penslinger med kvælstof-sennepsgas kan anvendes i perioder henover en lang årrække (> 10 år), hvis patienten har god effekt. Fagudvalget vurderer, at denne erfaring med rimelighed kan overføres på anvendelsen af chlormethin-gel.

Vedr. dosering og opbevaring: Fagudvalget er opmærksom på, at en tube med chlormethin-gel har en holdbarhed på 60 dage, og at minimumsforbruget i en behandlingsperiode derfor er ~0,5 tube om måneden, hvis man skal imødekomme dette. Fagudvalget vurderer, at en patient med < 30 % af huden afficeret maks. vil bruge 0,5 tube pr. måned, patienten modtager behandling.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

8. Referencer

1. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer. 2017;77:57–74.

2. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Ca. Blood. 2007;110(6):1713–22.

3. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. J Clin Oncol. 2010;28(31):4730–9.

4. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118(15):4024–35.

5. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv30-iv40.

6. Lindahl LM, Fenger-Gron M, Iversen L. Topical nitrogen mustard therapy in patients with mycosis fungoides or parapsoriasis. J Eur Acad Dermatol Venereol. 2013;27(2):163–8.

7. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA dermatology. 2013;149(1):25–32.

8. El Sayed H, Shalaby S, Abdel-Halim MRE, Aboelfadl DM, Samir N. Efficacy of doxycycline in the treatment of early stages of mycosis fungoides: a randomized controlled trial. J Dermatolog Treat. 2019;1–8.

9. Kim EJ, Geskin LJ, Querfeld C, Girardi M, Mink DR, Williams MJ, et al. Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study. Eur J Cancer. 2019;119:S39.

10. Kim EJ, Geskin L, Guitart J, Querfeld C, Girardi M, Musiek A, et al. Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study. J Am Acad Dermatol. 2020;83(3):928–30.

11. Quaglino P, Prince HM, Cowan R, Vermeer M, Papadavid E, Bagot M, et al.

Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol. 2021;184(4):722–30.

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)
Fagudvalgets sammensætning er listet, som det var gældende på tidspunktet for vurderingsrapportens udarbejdelse.

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Møller Pedersen *Forskningsansvarlig overlæge*	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Jakob Madsen *Ledende overlæge*	Region Nordjylland
Paw Jensen *Overlæge*	Region Nordjylland
Ida Blok Sillesen *Afdelingslæge*	Region Midtjylland
Adam Christian Vilmar *Afdelingslæge*	Region Syddanmark
Dorte Maegaard Tholstrup *Afdelingslæge*	Region Sjælland
Torsten Holm Nielsen *Afdelingslæge*	Region Hovedstaden
Michael Boe Møller *Overlæge*	Dansk Patologiselskab
Kathrine Bruun Svan *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Rikke Bech *Afdelingslæge*	Dansk Dermatologisk Selskab
Lise Lindahl *1. reservelæge*	Dansk Dermatologisk Selskab

Sammensætning af fagudvalg	
Maria Kamstrup *Afdelingslæge*	Dansk Dermatologisk Selskab
En patient/patientrepræsentant	Danske Patienter
Jørn Søllingvrå *Patient/patientrepræsentant*	Danske Patienter
Øvrige medlemmer, som har bidraget til arbejdet	**Udpeget af**
Jacob Haaber Christensen *Overlæge*	Region Syddanmark
Michael Pedersen *Overlæge*	Region Hovedstaden

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	28. september 2022	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 4. Vurdering af risiko for bias Lessin, 2013, Study 201, NCT00168064

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Forbehold	Studiepublikation og andet tilgængeligt materiale indeholder ikke tilstrækkelig information om randomiseringsprocessen. EPAR omtaler en fejl i randomiseringen på et af forsøgscentrene, hvor der deltog 18 patienter.
Effekt af tildeling til intervention	Forbehold	Der er tale om et 'observer'-blindet studie (= patienterne er ikke blindet). Dog er det tilsvarende behandlinger i begge arme, så det har sandsynligvis mindre betydning.
Manglende data for effektmål	Lav	Det er udført ITT-analyser. Der er begrænset og sammenligneligt frafald mellem armene.
Risiko for bias ved indsamlingen af data	Forbehold	Patienterne har kendskab til deres behandling, da blindingen næppe er opretholdt, idet der er tale om gel i den ene arm og salve i den anden arm. Dette kan påvirke bivirknings-registreringen. Vurdering af respons blev foretaget af blindet personale.
Risiko for bias ved udvælgelse af resultater, der rapporteres	Forbehold	Der findes ikke en offentligt tilgængelig protokol eller statistisk analyseplan.
Overordnet risiko for bias	Forbehold	

Tabel 5. Vurdering af risiko for bias El Sayed, 2019, NCT03454945

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Forbehold	Enkeltcenterstudie, hvor randomiseringen foregår ved brug af blindede kort. Det fremgår ikke, hvordan disse kort er opbevaret, og hvem der har haft adgang til dem.
Effekt af tildeling til intervention	Forbehold	Studiet er ikke blændet.
Manglende data for effektmål	Lav	Det er udført ITT-analyser. Der er intet frafald.
Risiko for bias ved indsamlingen af data	Forbehold	Studiet er ikke blændet. Dette kan påvirke bivirkningsregistreringen og livskvalitet.
Risiko for bias ved udvælgelse af resultater, der rapporteres	Forbehold	Der findes ikke en offentligt tilgængelig protokol eller statistisk analyseplan. Effektmålene er meget uklart defineret på clinicaltrials.gov, så det er vanskeligt at vurdere, om der har været en prædefineret intention i forhold til dataanalyse.
Overordnet risiko for bias	Forbehold	Forbehold for bias i randomiseringen og blindingen.

Application for the assessment of chlormethine gel (Ledaga®) for adult patients with mycosis fungoides cutaneous T-cell lymphoma

Application to the Danish Medicines Council

17 March 2021

Contents

1. Abbreviations

AE	Adverse events
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CSR	Clinical study report
CTCL	Cutaneous T-cell lymphoma
DLQI	Dermatology Life Quality Index
DMC	Danish Medicines Council
EE	Efficacy evaluable
EMA	European Medicines Agency
EOS	End of study
EPAR	European public assessment report
HADS	Hospital anxiety and depression score
HCL	Hydrochloride
HRQoL	Health-related quality of life
ITT	Intention to treat
MF	Mycosis fungoides
MF-CTCL	Mycosis fungoides cutaneous T-cell lymphoma
mSWAT	Modified Severity Weighted Assessment Tool
ORR	Objective response rate
PD	Progressive disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PUVA	Psoralen UV-A
QoL	Quality of life
RCT	Randomised controlled trial
Rt-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SD	Stable disease
TBSA	Total body surface area
TEAE	Treatment-emerged adverse event
TNMB	Tumour-nodes-metastatic-blood
US	United states
UV	Ultraviolet
UV-B	Ultraviolet-B
VAS	Visual analogue scale
VGPR	Very good partial response

2. Basic information

Table 1: Contact information.

Contact information	
Name	Fabian Schmidt
Title	Market Access and External Affairs Director – Recordati Rare Diseases
Area of responsibility	Primary contact person
Phone number	+33 787 41 66 09
E-mail	SCHMIDT.F@recordati.com

Table 2: Overview of chlormethine 0.02% gel.

Overview of the pharmaceutical	
Proprietary name	Ledaga
Generic name	Chlormethine gel (mechlorethamine, nitrogen mustard)
Marketing authorization holder in Denmark	Helsinn Birex Pharmaceuticals Ltd.
ATC code	L01AA05
Pharmacotherapeutic group	Alkylating agent
Active substance(s)	Chlormethine
Pharmaceutical form(s)	Topical gel 0.02% formulation
Mechanism of action	Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells and induces apoptosis, primarily through DNA alkylation (1). Chlormethine induces DNA alkylation by binding to N7 guanine residues (potentially N3 adenine residues). The binding forms cross-links between guanine residues on opposite DNA strands (2,3). The unrepaired inter-strand cross-links included by chlormethine in the cell DNA prevent DNA transcription and replication causing apoptosis (1,4,5)
Dosage regimen	Once daily topical administration of a thin layer of gel to affected areas (1)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Chlormethine gel is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients (1)
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes

Overview of the pharmaceutical	
Combination therapy and/or co-medication	None required
Packaging – types, sizes/number of units, and concentrations	Tubes of 60 g chlormethine 0.02% (160 μg/g) gel
Orphan drug designation	Yes.

3. Summary

Background

Recordati Rare Diseases has requested the Danish Medicines Council (DMC) to evaluate chlormethine 0.02% gel (Ledaga®) as standard treatment of adult patients with MF-CTCL. Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells and induces apoptosis, primarily through DNA alkylation (1). Currently, chlormethine is available at Aarhus University Hospital as a compounded preparation made from mechlorethamine HCL (Mustargen), but this formulation will soon be unavailable. Ledaga is a 0.02% chlormethine gel formulation and according to the summary of product characteristics (SmPC) on chlormethine gel, a thin layer should be administered once daily to affected areas. However, the actual dosing frequency vary between patients which was shown in a French real-world evidence study, where a dosing frequency of three times per week or one application every two days were observed.

Method

The DMC protocol for chlormethine 0.02% gel outlined two clinical questions; 1) what is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B, and PUVA in adult patients with early stage (I-IIA) MF CTCL, who have had inadequate effect of at least one optimised topical treatment and 2) what is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B, and PUVA in adult patients with stage IIB-IV MF-CTCL or adult MF-CTCL patients (regardless of stage) with patches and plaques in the head/neck regions and the genitals, who have had inadequate effect of at least one optimised topical treatment.

We conducted a systematic literature search using the search terms and criteria defined in the protocol. We were not able to identify any references including head-to-head comparisons of chlormethine 0.02% gel with any of the comparators outlined in the protocol. To answer clinical question 1, we conducted a narrative indirect comparison with data on chlormethine 0.02% gel from Study 201 and the PROVe study and data on psoralen UV-A (PUVA) from the study by El Sayed et al. 2019 (6,7). In the systematic literature search, we did not identify any references which would be appropriate to answer clinical question 2.

Results

The assessment of clinical question 1 was based on a narrative indirect comparison of chlormethine 0.02% gel and PUVA. At 12 months, the proportion of subjects with either complete response (CR) or partial response (PR) on mSWAT with chlormethine 0.02% gel was 61 out of 130 subjects (46.9%, 95% CI: 38.3%; 55.5%). In the PUVA study by El Sayed et al. 2019, 9 out of 18 subjects (50%, 95% CI: 27%; 73%) had CR or PR on mSWAT after three months. Duration of response was only assessed in Study 201 and only for response on Composite Assessment of Index Lesion Severity (CAILS). Kaplan-Meier curves showed a slow loss of response in the proportion of subjects who achieved either CR or PR measured with CAILS and that at least 90% of subjects maintained their responses for at least ten months. The only study assessing quality of life (QoL) with the Skindex-29 questionnaire was the PROVe study. The study found a difference in Skindex-29 scores between responders and non-responders of -10.7, -8.0, -9.6 at 12 months in the emotions, symptoms, and functioning domains, respectively. At 24 months, the differences in scores between responders and non-responders were -9.3, -10.0 and -8.6 in the respective domains. All differences were reported to be statistically significant (<0.001). Only Study 201 reported grade 3 and 4 adverse events (AEs). 33 out of 128 subjects (25.8%. 95% CI: 18.2%; 33.4%) and 3 out of 128 (2.3%, 95% CI: -0.3%; 5.0%) in the chlormethine 0.02% gel arm experienced a local dermal irritation of grade 3 and grade 4, respectively. Proportion of subjects with serious adverse events were reported in Study 201, where 14 out of 128 subjects (10.9%, 5.5%; 16.3%) experienced a serious adverse event in the chlormethine 0.02% arm.

4. Literature search

We conducted a systematic literature search with the search terms and criteria defined in the Danish Medicines Council (DMC) protocol for chlormethine gel. The DMC searched for literature where chlormethine gel has been compared directly to one or more of the comparators outlined in the protocol. The DMC did not identify any studies where a direct comparison of chlormethine gel and any of the outlined comparators have been conducted. The DMC provided a list of search terms to systematically search for literature which could be used for conducting an indirect comparison. The search terms and identified hits in PubMed and the Cochrane Library are provided in the Appendix section 8.1. We also consulted the public assessment reports (EPAR) from the European Medicines Agency (EMA) on chlormethine gel and the outlined comparators if such existed.

Databases and search strategy

We searched for relevant literature in PubMed and the Cochrane Library on 5 November 2020. We used the search terms given in the protocol. Search terms and number of hits in PubMed and the Cochrane library can be found in the Appendix section 8.1.

The inclusion and exclusion criteria defined in the protocol are listed in the Appendix in Table 19. We excluded articles with other patient populations than the ones specified in the protocol and articles not reporting results on at least one of the defined critical or important outcomes. We did not outline any strict exclusion criteria on study type due to the limited amount of available evidence relevant for the assessment. Figure 1 shows a PRISMA flowchart of the systematic literature search with the number of references identified and the process of selecting relevant references to use in the assessment of chlormethine gel.

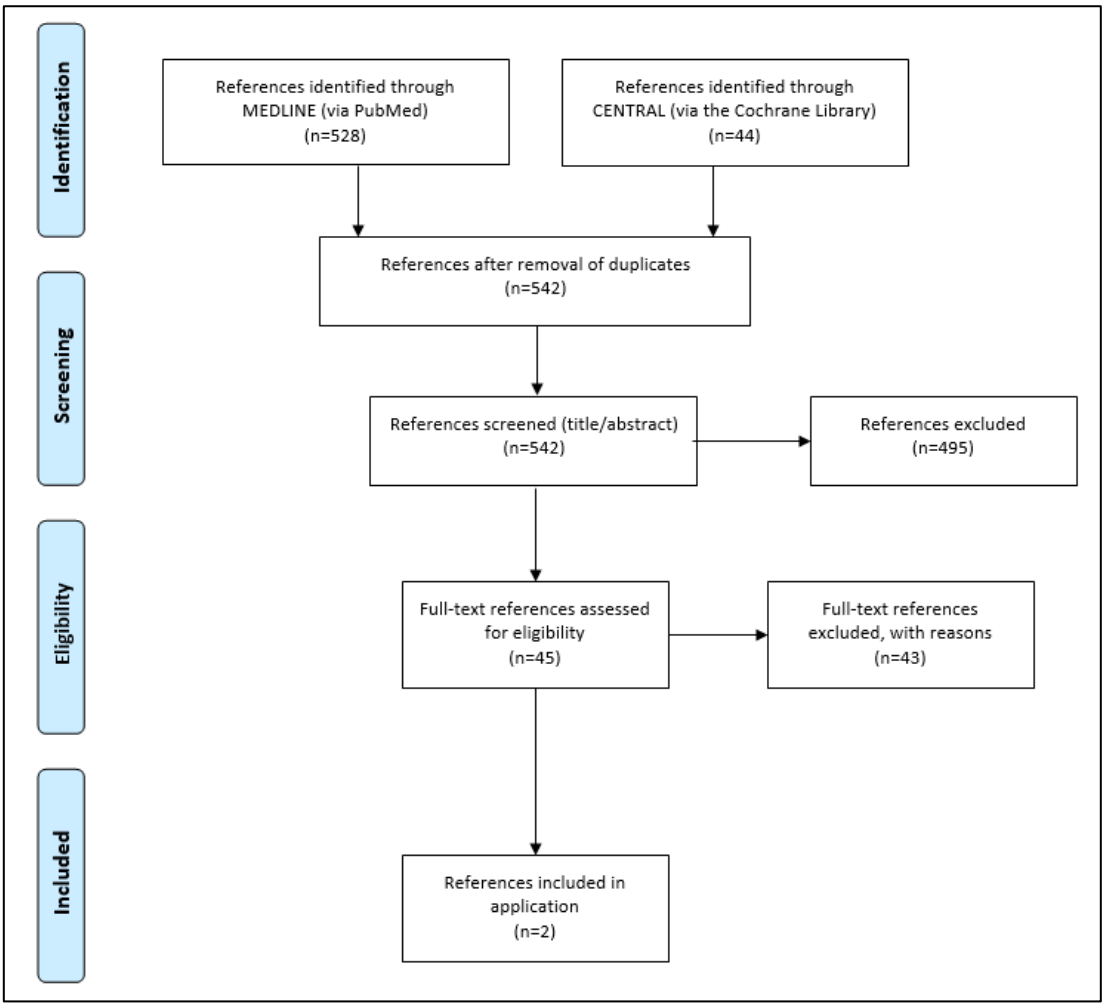


Figure 1: PRISMA flow-chart showing the systematic identification of relevant references to use in the application. The two references we ended up including are presented in the following sections.

4.1 Relevant studies

The systematic literature identified two references, which we included in the assessment of chlormethine gel and outlined comparators. Besides the two identified references, we included the PROVe study, which is currently only published as a research letter and an abstract by Kim et al. 2020 and Kim et al. 2019, respectively (8,9). The included studies are presented in Table 3.

Table 3: Overview of the relevant references.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question*
Title: Topical Chemotherapy in Cutaneous T-cell lymphoma. Positive results of a Randomised, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02% Gel in Mycosis Fungoides. Author: Lessin et al. 2013. Journal and year: Jama Dermatol. 2013.	Study 201	NCT00168064	Start: May 2006 End: August 2020	Clinical question 1
Title: Efficacy of Doxycycline in the Treatment of Early Stages of Mycosis Fungoides, a Randomized Controlled Trial. Author: El Sayed et al. 2019. Journal and year: Journal of Dermatological treatment, 2019.	Efficacy of Doxycycline in the Treatment of Early Stages of Mycosis Fungoides: A Randomized Controlled Trial	NCT03454945	Start: March 2017 End: April 2019	Clinical question 1
Title: Efficacy and quality of life (QoL) in patients treated with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study (Abstract) Author: Kim et al. 2019. Journal and year: European Journal of cancer 2019.	PROVe	NCT02296164	Start: November 2014 End: October 2018	Clinical question 1

*when multiple clinical questions are defined in the protocol.

4.2 Main characteristics of included studies

In this section, we present the main characteristics of the studies used in the comparative analyses. The systematic literature search did not identify any studies for topical corticosteroids or narrowband UV-B in the patient population or outcomes outlined in the protocol.

Information on chlormethine 0.02% gel came from the EPAR, the clinical study report (CSR) and publication by Lessin et al. 2013 (6) on Study 201 and an abstract and research letter on the PROVe study by Kim et al. 2019 (9) and Kim et al. 2020 (8), respectively. Information on PUVA came from the publication by El Sayed et al. 2019 (7). Additional study information, such as baseline characteristics, outcomes and methods of analysis, can be found in Section 8.2 in the Appendix.

4.2.1 Comparability of Study 201 and the study by El Sayed et al.

An overview of the main study characteristics is provided in Table 4. In terms of the study populations, both studies included patients with early stages of MF-CTCL, the overall ages of patients were similar in the two studies and both studies did not allow any concomitant therapies. Moreover, patients in Study 201 had to have received at least 1 prior treatment to be included and patients in the EL Sayed et al. study had to undergo a wash-out period from all treatments before being eligible for enrolment in the study. Patients had been diagnosed with MF-CTCL for 2-25 years in the El Sayed et al. study, and we therefore assumed that most patients had received previous topical treatments before enrolment in the study. In general, patients in the El Sayed et al. study had been diagnosed with MF-CTCL for longer than patients in Study 201 and the gender distribution differed in the two studies. However, we regard the patient populations in the two studies to be comparable. El Sayed et al. recruited more IB patients compared to Study 201, which is in line with the place in therapy of phototherapy.

In terms of study design, Study 201 and El Sayed et al. had a similar design, as they were both randomised and active-controlled. The primary outcome in both studies was clinical response rate and both studies measured response with changes on mSWAT from baseline and both studies used a strictly comparable clinical endpoint. However, the follow-up period in Study 201 was longer than the follow-up period in the El Sayed et al. study, which must be taken into consideration when evaluating the results from the narrative comparison of the study outcomes. Furthermore, 260 patients were randomised 1:1 to either chlormethine gel 0.02% or chlormethine ointment 0.02% in Study 201, while only 36 patients were randomised 1:1 to doxycycline or PUVA in the EL Sayed study.

Even though there are some differences in terms of patient populations and study design in the two studies, we believe that the two studies constitute the best available evidence to answer the clinical questions outlined by the expert committee.

Table 4: Overview of the main characteristics in the included studies. Sources:

Parameter	Study 201	El Sayed et al. 2019	The PROVe study
Study design/type	Phase II/III, randomised, active-controlled trial	Randomised, active-controlled trial	Prospective, observational trial
Intervention	Chlormethine 0.02% gel	PUVA	Chlormethine gel (Valchlor)
Comparator	Chlormethine 0.02% ointment	doxycycline	None

Follow-up time	12 months	Three months	Two years
Number of subjects	Total of 260. 130 subjects randomised to each arm.	Total of 36. 18 subjects randomised to each arm.	298 enrolled.
Age	18–64 years: 93 (72%) 65–74 years: 29 (22%) ≥75 years: 8 (6%)	43.28 years (SD: ±10.18)	62 (21-90)
Gender distribution	60% male and 40% female	5 males (27.8%) and 13 females (72.2%)	60.1% male and 39.9% female
Concomitant treatments	No concomitant therapies (especially topical corticosteroids) were allowed, and no additional skin-directed or systemic therapies were used in the case of unresponsive or progressive disease	No concomitant therapies were allowed except for Vaseline topical application (if needed)	Concomitant therapies were allowed, both skin-directed and systemic therapies
Stage distribution			
IA	76 (59%)	2 (11.1%)	125 (41.9%)
IB	52 (40%)	13 (72.2%)	78 (26.2%)
IIA	2 (1%)	2 (11.1%)	9 (3.0%)
IIB	0	0	19 (6.4%)
III	0	0	5 (1.7%)
IV	0	0	6 (2.0%)
Unknown	0	0	56 (18.8%)
Duration of disease	<6 months: 47 (36.2%) 6 months-1 year: 18 (13.8%) 1 year-2 years: 14 (10.8) ≥2 years: 51 (39.2%)	Median: 9.50 years Range: 2-25 years	At enrolment: median of 2.9 years (range: 0.1, 48.3)

4.2.2 Study 201

Study 201 study was a phase II, multicentre, randomised, active-controlled, non-inferiority, single-blinded (observer) trial comparing chlormethine 0.02% gel with chlormethine 0.02% compounded ointment. Study 201 consisted of two treatment arms:

- chlormethine 0.02% gel once daily for up to 12 months; and

- chlormethine 0.02% ointment once daily for up to 12 months.

Chlormethine gel was applied once daily. According to the EPAR, subjects with stage IA disease were generally instructed to apply treatment to all affected lesions. Full-body application (beside the area around the eyes and mucous membranes) was generally instructed in subjects with either stage IB or IIA MF, or if the severity of new lesions developing after treatment initiation met the criteria for progressive disease (≥25% worsening). The duration of treatment was 12 months unless disease progression, treatment-limiting toxicity, concomitant illness or any change in health status necessitated discontinuation of study therapy. After the 12 months, subjects were followed for an additional 12 months to assess the potential risk of developing cutaneous tumours. A temporary reduction in daily application frequency (every other day or less frequently) was permitted if skin adverse events (AEs) emerged. Tumour response and AEs were assessed every month between months one and six and every two months between months seven and 12. (6)

Subjects with MF-CTCL having persistent or recurrent stage IA, IB or IIA disease and no history of progression beyond T2N1M0B0 (which equals stage IIA in the tumour, nodes, metastasis, and blood (TNMB) classification system) with at least one prior treatment were eligible for the study. A total of 260 subjects were enrolled, and 130 subjects were randomised to each treatment arm (the intention-to-treat (ITT) population). 255 subjects (98.1%) received at least one application of study drug (five subjects were never treated) and 81 subjects (62%) in the gel arm and 86 subjects (66%) in the ointment arm completed the 12-month study period, respectively.

The 255 subjects who received at least one application of study drug were included in the safety analysis set (128 subjects in the gel arm and 127 subjects in the ointment arm). Besides the five subjects that were never treated, 88 treated subjects (47 subjects in the chlormethine gel arm and 41 subjects in the chlormethine ointment arm) discontinued the study prematurely. The reasons for discontinuing treatment prematurely were as follows:

- treatment-limiting toxicity (21 subjects in gel arm and 16 subjects in ointment arm);
- other AEs (five subjects in the gel arm and six subjects in the ointment arm);
- lack of effect (four subjects in the gel arm and four subjects in the ointment arm);
- subjects' best interest (two subjects in gel arm and two subjects in ointment arm);
- concurrent illness (four subjects in gel arm and three subjects in ointment arm);
- withdrew consent (three subjects in gel arm and four subjects in ointment arm);
- non-compliance (two subjects in gel arm three subjects in ointment arm);
- lost to follow-up (four subjects in gel arm and three subjects in ointment arm); and
- other reasons (four subjects in gel arm and three subjects in ointment arm).

An overview of the subject disposition is provided in Figure 2.

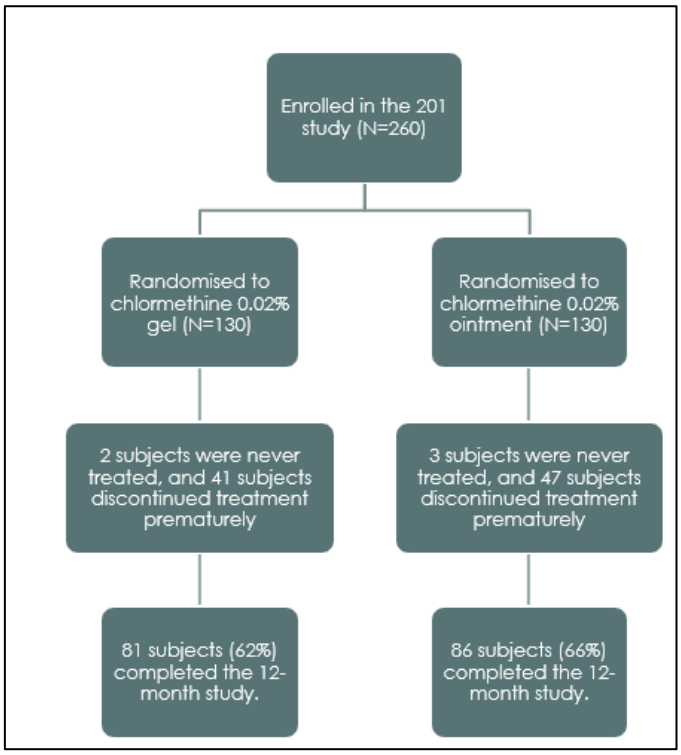


Figure 2: The subject disposition in Study 201. Five patients never received treatment (two in gel arm and three in ointment arm): four patients had disease that progressed between screening and baseline and were no longer eligible for the trial and one randomised patient withdrew consent prior to starting the study drug.

4.2.3 The PROVe study

The PROVe study is a multi-centre, prospective, observational, United States (US)-based drug study aiming to assess clinical characteristics, treatment patterns, response assessment patterns and healthcare utilisation in MF-CTCL, safety of chlormethine gel and patient reported outcomes focusing on health-related quality of life (HRQoL) in MF-CTCL. Patients were followed prospectively for a maximum of two years from the date of enrolment until the end of study.

In this cohort study, 301 adult patients with MF-CTCL actively using Valchlor (US brand name for chlormethine 0.02%) were enrolled at 41 US sites. Patients were monitored for up to two years, regardless of treatment discontinuation. Standard of care visit routine information (clinical characteristics, treatment patterns, response, AEs, HRQoL) were collected. At the time of the analysis, 298 patients were evaluable. Information on the patient characteristics are presented in Table 24. During Valchlor treatment, 48% used concomitant therapies comprising topical corticosteroids in 24%, phototherapy in 12% and systemic retinoids in 10%. Of the cohort, 79% continued Valchlor treatment at 12 months.

An overview of the dosing frequency is provided in Table 5. Most subjects (~75%) applied Valchlor once daily. A dose frequency change occurred in some subjects. The reason for changing the dose frequency was physician decision in 26%, complete response in 7% and AEs in 20%. Other observed dosing frequencies were every two days in 38%, every three days in 16%, once weekly in 9%, and daily Monday through Friday in 10%. At the time of the analysis, 39% of patients had discontinued Valchlor treatment due to AEs (9%), complete response (4%) or physician's decision (7%). (8)

Table 5: Dosing frequencies in the PROVe study. Source: Kim et al. 2020 (8).

Dosing frequency	PROVe study (N=298)
Once daily – no. (%)	222 (74.5%)
Five times weekly – no. (%)	30 (10.1%)
Every two days – no. (%)	112 (37.6%)
Every three days – no. (%)	49 (16.4%)
Once weekly – no. (%)	26 (8.7%)
Less frequent than once weekly (monthly; as needed; unknown – no. (%)	34 (11.4%)

4.2.4 The study by El Sayed et al. 2019

The study by El Sayed et al. 2019 was a phase III, randomised, active-controlled trial. The study consisted of two treatment arms:

- doxycycline; and
- PUVA.

40 adult subjects with MF-CTCL were assessed based on certain inclusion and exclusion criteria for their eligibility to be enrolled in the study. Inclusion and exclusion criteria are presented in Table 25. Included in the study were adults (age above 18) of both sexes with early stages of MF-CTCL (IA-IIA). Accordingly, and based on a predefined calculated sample size, 36 of the 40 recruited subjects were enrolled in the therapeutic phase. A wash-out period of at least four weeks from any relevant topical or systemic treatment that could affect the course of MF was adopted.

All 36 patients were randomly assigned in a 1:1 ratio, using blinded cards, to either one of the two parallel arms of the trial: doxycycline 100 mg oral capsules twice daily (18 subjects) or PUVA (0.5 mg/kg 8-methoxypsoralen, starting dose: 1–3 J/cm^2 according to Fitzpatrick's skin type and increments of increase every other session of 0.5 J/cm^2 according to the degree of erythema and based on the guidelines of the Phototherapy Unit, Dermatology Department, Faculty of Medicine, Cairo University, Qasr El Eyni University Hospital). An overview of the subject disposition is presented in Figure 3. End of study (EOS) was defined as achieving complete response or a maximum of three months (12 weeks) of treatment. At both day 0 and at EOS, all 36 randomised subjects were clinically assessed by a blinded senior investigator using standardised clinical scoring systems for MF-CTCL, which included: modified severity-weighted assessment tool (mSWAT) and composite assessment of index lesion severity (CAILS). Moreover, pruritus was assessed using a visual analogue scale (VAS) from 0 to 10, where 0 = no pruritus and 10 = worst imaginable pruritus, and patients' satisfaction was assessed using dermatology life quality index (DLQI) (7).

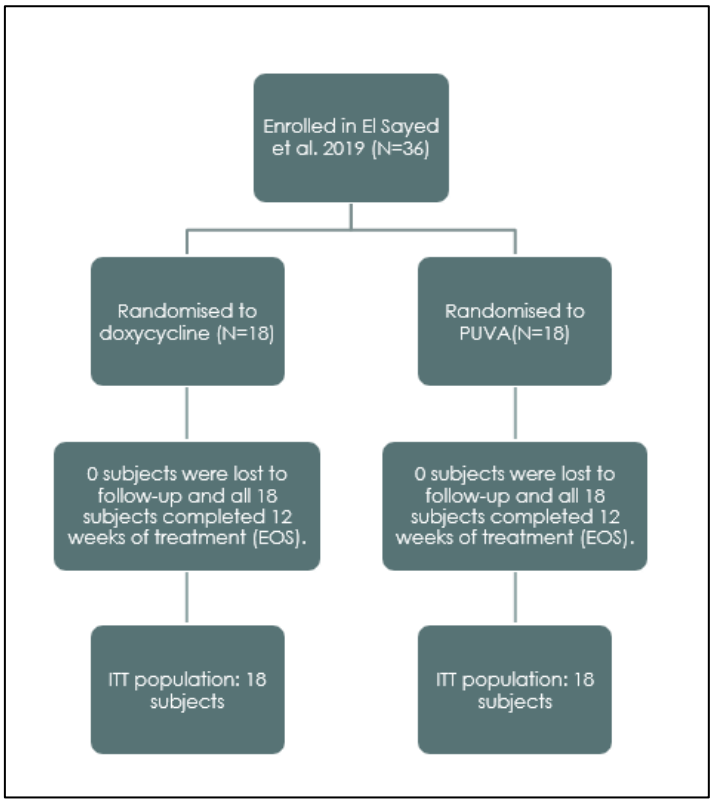


Figure 3: The subject disposition in El Sayed et al. 2019 (7)

5. Clinical questions

5.1 Clinical question 1: what is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B, and PUVA in adult patients with early stages (I-IIA) of MF-CTCL, who have had inadequate effect of at least one optimised topical treatment?

5.1.1 Presentation of relevant studies

In the systematic literature search, we identified Study 201 published by Lessin et al. 2013 (6) and the study by El Sayed et al. 2019 (7). There is no standard definition of "inadequate effect" but according to consulted physicians it would be either no CR or no PR upon treatment or relapse after initial CR or PR. The consulted physicians are the Danish Professor Lars Iversen, Professor Papadavid, Greece, and Professor Bagot, France, who are all very experienced in treating MF-CTCL patients and who works at big treatment centres.
Study 201 explicitly states that it included patients who have previously received topical treatments, which we assume equivalent to the patient population outlined in the protocol. There were no comparator studies identified in the

systematic literature search that explicitly stated that included patients had experienced inadequate effect of an optimised topical treatment.

El Sayed et al. 2019 stated that patients had to undergo a wash-out period of at least four weeks from any topical or systematic treatment before entering the study. Based on this, we assume that patients had at least previously received topical treatments and could match the patient population outlined in the protocol.

The systematic literature search did not identify any studies containing a direct comparison of chlormethine 0.02% gel and any of the comparators outlined in the protocol. Furthermore, it was not possible to identify any studies assessing the efficacy and safety of narrowband UV-B or topical corticosteroids in the patient population outlined in the protocol. Therefore, the answer to clinical question 1 is based on a narrative indirect comparison of chlormethine 0.02% gel and PUVA. The narrative indirect comparison is informed by Study 201 and publication by Lessin et al. 2013, the abstract and research letter by Kim et al. 2019 and Kim et al. 2020, respectively, and the study by El Sayed et al. 2019.

5.1.2 Results per study – Study 201

Reduction of skin symptoms – critical outcome

Reduction of skin symptoms is measured as the proportion of patients who achieve response (either CR or PR) on mSWAT. The key secondary endpoint in Study 201 was mSWAT, which was determined by weighting body surface area (BSA) involvement for patches, plaques, and tumours, and summing the scores for each category. Response rate was defined as ≥50% improvement in the mSWAT, which was derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity-weighting factor (1=patch, 2=plaque, 4=tumour). The mSWAT score is the sum of (1 × patch %BSA) + (2 × plaque %BSA) + (4 × tumour/ulcer %BSA). Response was defined as ≥50% improvement in the baseline mSWAT score on two or more consecutive observations over at least four weeks. (10)

mSWAT scores were calculated at baseline (day 1). At each study visit, the tumour response was determined using standard oncology criteria for complete response (100% improvement, with a score of 0), partial response (50% to 100% reduction from the baseline score) and stable disease (50% reduction from the baseline score). Confirmed responses were those observed for at least four weeks. The response categories for mSWAT are presented in Table 6

Table 6: Response categories for mSWAT in Study 201. Source: EPAR on chlormethine (10).

Outcome	Change from baseline
Response	
Complete response (CR)	Score of 0
Partial response (PR)	>50% reduction from baseline but not 0
Non-response	
Stable disease (SD)	<50% reduction or <25% increase from baseline

Progressive disease (PD)	≥25% increase from baseline
Unevaluable	No post-baseline data available

Results

Results on mSWAT response rates are presented in Table 7. In Study 201, response (either CR or PR) was achieved by 61 subjects (46.9%, 95% CI: 38.3%; 55.5%) in the chlormethine 0.02% gel arm. Nine subjects (6.9%, 95% CI: 2.6%; 11.3%) achieved CR and 52 subjects (40.0%, 95% CI: 31.6%; 48.4%) achieved PR.

Table 7: mSWAT response rates from Study 201 at 12 months (ITT population)

	Chlormethine 0.02% gel (N=130)	Chlormethine 0.02% ointment (N=130)	Source
Overall (CR+PR) – no. (%)	61 (46.9%) 95% CI: 38.3%; 55.5%	60 (46.2%) 95% CI: 37.6%; 54.7%	EPAR (10)
Complete response (CR) – no. (%)	9 (6.9%) 95% CI: 2.6%; 11.3%	4 (3.1%) 95% CI: 0.1%; 6.0%	
Partial response (PR) – no. (%)	52 (40.0%) 95% CI: 31.6%; 48.4%	56 (43.1%) 95% CI: 34.6%; 51.6%	
No response – no. (%)	69 (53.1%) 95% CI: 44.5%; 61.7%	70 (53.8%) 95% CI: 45.3%; 62.4%	

Quality of life – critical outcome

QoL was not an outcome in Study 201; therefore, we are not able to present any data.

Duration of response – Important outcome

Duration of response based on mSWAT score was not an outcome in Study 201, but duration of response based on CAILS score was reported. It was defined as the time from the first appearance of the response to the first assessment where the response was no longer apparent (i.e. CAILS score showed <50% improvement from baseline).
Duration of response based on CAILS score in the ITT population was analysed in subjects who achieved a CAILS response, which was 76 subjects in the chlormethine 0.02% gel arm and 62 subjects in the 0.02% ointment arm using the study protocol definition (progressive disease or loss of response of <50% improvement from the baseline score) and the consensus definition (progressive disease or increase from score greater than the nadir plus 50% baseline score) from Olsen et al. 2011 (11).

Results

The same duration of response was seen with both above-mentioned definitions in all but eight subjects (four in each treatment arm), who had a longer duration of their response using the consensus definition. 65 of 76 subjects (85.5%, 95% CI: 77.6%; 93.4%) in the gel arm and 51 of 62 subjects (82.3%, 95% CI: 72.7%; 91.8%) in the ointment arm maintained their response through the end of the trial (12 months). (6)

Kaplan-Meier curves for the duration of CAILS response is presented in Figure 4. The Kaplan-Meier curves show that at least 90% of responses will be maintained for at least ten months. The log-rank test showed no statistically significant difference (p-value: 0.48) between the 0.02% gel and 0.02% ointment in Study 201 (6). The median duration of response was not reached during the study period of 12 months.

Table 8: The proportion of subjects who maintained their CAILS response throughout the trial duration (12 months) (ITT population). N in this table represents the number of subjects who achieved a CAILS response (either CR or PR).

	chlormethine gel (N=76)	chlormethine ointment (N=62)	Source
Maintained CAILS response at study end (12 months) – no. (%)	65 (85.5%)	51 (82.3%)	Lessin et al. 2013 (6)
95% CI	77.6%; 93.4%	72.7%; 91.8%	

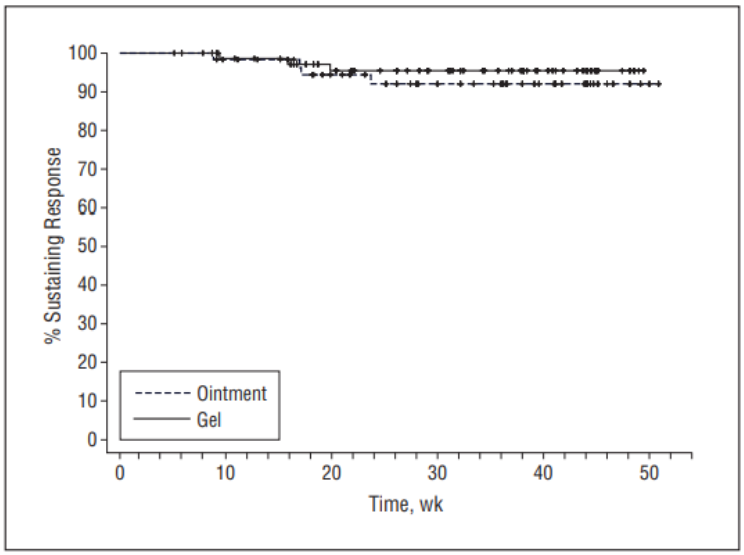


Figure 4: The Kaplan-Meier curves for the duration of CAILS response in the gel arm and ointment arm (ITT population). Source: Lessin et al. 2013 (6).

Adverse events – important outcome

The expert committee has requested data on the proportion of subjects who experience a serious AE (SAE). In Study 201, 108 subjects (84.4%, 95% CI: 78.1%; 90.7%) in the gel arm and 115 subjects (90.6%, 95% CI: 85.5%; 95.6%) in the ointment arm experienced at least one AE. 14 subjects (10.9%, 95% CI: 5.5%; 16.3%) in the gel arm and 11 subjects (8.7%, 95% CI: 3.8%; 13.6%) in the ointment arm experienced a SAE. Most AEs in both treatment arms were skin-related, characterised mainly as local dermatitis (skin irritation). Results are presented in Table 9.

Table 9: Summary of all AEs observed in Study 201 (safety analysis set). Source: EPAR on chlormethine.

	Chlormethine 0.02% gel (N=128)	Chlormethine 0.02% ointment (N=127)	All subjects (255)
Subjects with AEs – no. (%)	108 (84.4%)	115 (90.6%)	223 (87.5%)

95% CI	78.1%; 90.7%	85.5%; 95.6%	83.4%; 91.5%
Subjects with a serious AE – no. (%)	14 (10.9%)	11 (8.7%)	25 (9.8%)
95% CI	5.5%; 16.3%	3.8%; 13.6%	6.2%; 13.5%

The expert committee has also requested data on the proportion of subjects who experience grade 3 and grade 4 AEs. The only AEs categorised as such in Study 201 were drug-related skin and subcutaneous AEs, presented in Table 10. 33 subjects (25.8%, 95% CI: 18.2%; 33.4%) in the gel arm and 21 subjects (16.5%, 95% CI: 10.1%; 23.0%) in the ointment arm experienced a local dermal irritation of a grade 3 severity, respectively. Three subjects (2.3%, 95% CI: -0.3%; 5.0%) in the gel arm and one subject (0.8%, 95% CI: -0.7%; 2.3%) in the ointment arm experienced a local dermal irritation of a grade 4 severity, respectively. The incidence of skin irritation was significantly higher in the gel arm (p-value = 0.04). (6)

Table 10: The proportion of subjects in the two treatment arms in Study 201 who experienced grade 3 and grade 4 drug-related skin and subcutaneous AEs. Source: EPAR on chlormethine.

	Chlormethine 0.02% gel	Chlormethine 0.02% ointment
Local dermal irritation grade 3 (moderate to severe) – no. (%)	33 (25.8%)	21 (16.5%)
95% CI	18.2%; 33.4%	10.1%; 23.0%
Local dermal irritation grade 4 (severe) – no. (%)	3 (2.3%)	1 (0.8%)
95% CI	-0.3%; 5.0%	-0.7%; 2.3%

5.1.3 Results per study – The PROVe study

The PROVe study was used to assess the quality of life (QoL) outcome outlined in the protocol, because the PROVe study assessed the QoL of MF-CTCL patients with the SkinDex-29 questionnaire.

Quality of life – critical outcome

The SkinDex-29 questionnaire is a questionnaire developed for measuring QoL in dermatological conditions. It consists of three subscales: skin-related, emotional and functional symptoms. The total score ranges from 29 to 116 and is in the evaluation of QoL transformed to a linear scale of 0 to 100, where higher scores indicate worse QoL. (12)

Results

Changes in Skindex-29 scores were reported based on whether subjects were responders (≥50% reduction in pre-enrolment baseline %BSA coverage of lesions) or non-responders at 12 months and 24 months.

In the whole study population over the 12-month period, weighted mean Skindex-29 scores were lower in responders (26.4, 26.8 and 13.2) versus non-responders (37.1, 34.8 and 22.8) for the same three domains, respectively. Over the

24-month period, Skindex-29 scores were also lower in responders versus non-responders (26.4, 25.6 and 14.0 versus 35.7, 35.6 and 22.6 for emotions, symptoms and functioning, respectively). All scores were statistically significantly improved (p<0.001) in responders versus non-responders. Response rats by Results are presented in Table 11.

Table 11: Skindex-29 scores from the PROVe study. The table shows the number of patients included in the responder and non-responder analyses at 12 months and at 24 months, respectively. Source: Kim et al. 2019 (abstract) (9).

Skindex-29 domain	Responder, mean Skindex-29 score		Non-responder, mean Skindex-29 score		p-value*
	12 months (n=106)	24 months (n=42)	12 months (n=107)	24 months (n=32)	
Emotions	26.4	26.4	37.1	35.7	<0.001
Symptoms	26.8	25.6	34.8	35.6	<0.001
Functioning	13.2	14.0	22.8	22.6	<0.001

*the p-value for responders versus non-responders for both 12 and 24 months.

5.1.4 Results per study – The study by El-Sayed et al. 2019

Reduction of skin symptoms – critical outcome

The primary treatment outcome at EOS was to compare the therapeutic efficacy of doxycycline versus PUVA, defined as the objective response rate (ORR) measured according to changes in mSWAT from baseline. Table 12 shows the objective response definitions based on changes in mSWAT.

Table 12: Response definitions based on changes in mSWAT. Source: El Sayed et al. 2019 (7).

Response	Definition
Complete response (CR)	100% clearance of skin lesion
Partial response (PR)	50–99% clearance of skin disease from baseline without new tumours (T3) in patients with T1, T2 or T4 only skin disease
Stable disease	<25% increase to 50% clearance in skin disease from baseline without new tumours (T3) in patients with T1, T2, or T4 only skin disease
Progressive disease (PD)	≥25% increase in skin disease from baseline or New tumours (T3) in patients with T1, T2 or T4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score

Relapse	Any disease recurrence in those with complete response

Results

Response (either CR or PR) in the PUVA arm was achieved by nine subjects out of 18 (50%). No subjects (0%) in the PUVA arm achieved CR, while nine subjects (50%, 95% CI: 27%; 73%) in the PUVA arm achieved PR. Results are presented in Table 13.

Table 13: Results on the mSWAT outcome in the study by El Sayed et al. 2019 (7) at EOS (ITT population).

	Complete response (N=18)	Partial response (N=18)	CR+PR (N=18)
PUVA arm – no. (%)	0 (0%)	9 (50%)	9 (50%)
95% CI	0%; 0%	27%; 73%	27%; 73%
Doxycycline arm – no. (%)	0 (0%)	2 (11.1%)	2 (11.1%)
95% CI	0%; 0%	-3%; 26%	-3%; 26%

Duration of response - important

Duration of response was not assessed in the study by El Sayed et al. 2019; therefore, we are unable to present any data on this outcome.

Adverse events – important outcome

The study by El Sayed et al. 2019 (7) did not classify AEs as grade 3 or grade 4 and did not report any SAEs. Therefore, we are not able to present the AE data requested by the expert committee in the protocol.

5.1.5 Comparative analyses

It was not possible to conduct a direct comparison of chlormethine gel and any of the outlined comparators due to a lack of studies comparing the alternatives head-to-head. Furthermore, it was not possible to conduct an indirect comparison using e.g. Buchers' method or a network meta-analysis due to methodological differences in the included studies (see Table 4). Data on narrowband UV-B and topical corticosteroids could not be identified for the relevant patient population or relevant outcomes. Therefore, we present a narrative indirect comparison of chlormethine 0.02% gel and PUVA. The narrative indirect comparison was informed by Study 201 published in Lessin et al. 2013, the PROVe study and the study by El Sayed et al. 2019.

No data on duration of response or QoL was presented for PUVA in the study by El Sayed et al. 2019 and therefore, we are not able to present a narrative indirect comparison of this outcome.

Reduction of skin symptoms

mSWAT response rates were reported at 12 months in Study 201 and at three months in the study by El Sayed et al. 2019. After 12 months, 61 out of 130 subjects (46.9%, 95% CI: 38.3%; 55.5%) treated with chlormethine 0.02% gel had

achieved either CR or PR in Study 201. After three months, 9 out of 18 subjects (50%, 95% CI: 27%; 73%) treated with PUVA had achieved either CR or PR in the study by El Sayed et al. 2019.

Table 14: Narrative indirect comparison of response rates in mSWAT from Study 201 (6) and the study by El Sayed et al. 2019 (7). Results on chlormethine 0.02% gel is at 12 months and results on PUVA is at three months.

	Chlormethine 0.02% gel arm from Study 201 (N=130), at 12 months	PUVA arm in El Sayed et al. 2019 (N=18), at three months
Overall (CR+PR) – no. (%)	61 (46.9%) 95% CI: 38.3%; 55.5%	9 (50%) 95% CI: 27%; 73%
Complete response (CR) – no. (%)	9 (6.9%) 95% CI: 2.6%; 11.3%	0 (0%) 95% CI: 0%; 0%
Partial response (PR) – no. (%)	52 (40.0%) 95% CI: 31.6%; 48.4%	9 (50%) 95% CI: 27%; 73%

Duration of response

As mentioned, it was not possible to identify any studies for chlormethine 0.02% gel or comparators where the duration of response (CR or PR) with mSWAT were reported. However, Study 201 on chlormethine gel reported duration of response (CR or PR) with CAILS, which we have reported. The argument for reporting this, even though it does not match what the expert committee has outlined in the protocol, is that CAILS is also recommended as a relevant effect measure in clinical trials and is mentioned in the guidelines from the International Society for Cutaneous Lymphomas (ISCL), US Cutaneous Lymphoma Consortium and EORTC Cutaneous Lymphoma Task Force Consensus (11). We cannot compare the results from Study 201 with data on the comparators, but we can emphasise that the Kaplan-Meier curves presented in Figure 4 show a very slow loss of treatment response in the proportion of subjects who achieved either CR or PR measured with CAILS and that at least 90% of subjects maintained their responses for at least ten months.

Quality of life

It was not possible to conduct a comparative analysis of chlormethine gel and PUVA in the QoL outcome due to lack of evidence. Furthermore, the baseline Skindex-29 scores of subjects in the PROVe study were not reported; thus, we are unable to estimate the proportion of subjects with a 10-point reduction in the Skindex-29 score or mean change in Skindex-29 score from baseline to the maximum follow-up time.

No baseline data for QoL is available because it was difficult to collect baseline data of QoL for all the patients, considering that the PROVe was an observational study, collecting real world evidence on the use of chlormethine gel, with no specific protocol restrictions/indication on data collection. Many patients entered the PROVe study while they were already using Valchlor (41% was started <3 months before study enrollment). Therefore, differently from a standard clinical trial, the collection of data, including the Baseline of the QoL questionnaires, was in some cases recorded after the patients initiated the treatment (13).

However, the results from Kim et al. 2021 (13) showed that subjects who achieved a response (a ≥50% reduction in pre-enrolment baseline BSA percentage coverage of lesions) had a significant improvement in their QoL measured with the Skindex-29 questionnaire, compared to those who did not achieve a response (see Table 11). Table 15 shows the differences in the scores between responders (as defined above) and non-responders in the three domains of the Skindex-29 questionnaire. The results show that a ≥50% reduction in pre-enrolment baseline BSA percentage coverage of lesions is associated with an improvement in subjects' QoL.

Table 15: Differences in the scores of responders versus non-responders in the domains of the Skindex-29 questionnaire from the PROVe study. Source: Kim et al. 2021 .

	Emotions	Symptoms	Functioning	p-value*
Difference in mean Skindex-29 score between responders and non-responders, 12 months	-10.7	-8.0	-9.6	<0.001
Difference in mean Skindex-29 score between responders and non-responders, 24 months	-9.3	-10.0	-8.6	<0.001

*p-value for responders versus non-responders for both 12 and 24 months.

Adverse events

Information on proportion of subjects experiencing SAEs were reported in Study 201. 14 subjects (10.9%, 95% CI: 5.5%; 16.3%) in Study 201 experienced a SAE while receiving treatment with chlormethine gel.

Table 16: Presentation of SAEs observed in Study 201 (safety analysis set).

	Chlormethine 0.02% gel (N=128)
Subjects with a serious AE – no. (%)	14 (10.9%)
95% CI	5.5%; 16.3%

The expert committee has also requested data on the proportion of subjects who experience grade 3 and grade 4 AEs. The only AEs categorised as such in Study 201 were drug-related skin and subcutaneous AEs, presented in Table 10. 33 subjects (25.8%, 95% CI: 18.2%; 33.4%) in the gel arm experienced a local dermal irritation of a grade 3 severity, and three subjects (2.3%, 95% CI: -0.3%; 5.0%) experienced a local dermal irritation of a grade 4 severity.

Table 17: The proportion of subjects in the chlormethine gel arm in Study 201 who experienced grade 3 and grade 4 drug-related skin and subcutaneous AEs. Source: EPAR on chlormethine.

	Chlormethine 0.02% gel
Local dermal irritation grade 3 (moderate to severe) – no. (%)	33 (25.8%)
95% CI	18.2%; 33.4%
Local dermal irritation grade 4 (severe) – no. (%)	3 (2.3%)
95% CI	-0.3%; 5.0%

Discussion of the comparability of the results from the studies

The only clinical outcome where data was comparable for both Study 201 and El Sayed et al. was reduction in skin symptoms on mSWAT. For all the other outcomes, only chlormethine gel data was available and therefore, these will not be included in the discussion of the comparability of the results.

A difference between the two studies used in the assessment of the outcome “reduction in skin symptoms” was the follow-up period. The follow-up period in Study 201 was longer (12 months) than in the study by El Sayed et al. (three months). The shorter follow-up period in the El Sayed study is not surprising when considering the treatment regimen of PUVA e.g. the duration of a treatment cycle with PUVA. According to the Danish physician Lars Iversen, the treatment regimen (and duration) of phototherapy is very individual between patients. Usually, patients receive phototherapy three times per week for 10 weeks (25-30 treatments) and some then continue with a reduced treatment frequency. He estimates that most patients have 40-50 treatments in total. Therefore, we assume that most patients receive the maximum treatment effect within a time period around the follow-up period in the El Sayed et al. study. Thus, we do not expect to see an increased treatment effect of PUVA if the follow-up time was 12 months. It should also be mentioned that long exposures to PUVA increase the carcinogenicity risk and long exposure is therefore not recommended. Moreover, the studies included patients with the same stages of MF-CTCL and approximately the same ages. The different gender distribution in the two studies was assumed to not have an impact on the outcome. When putting it all together, we regard the results on the clinical outcome to be comparable.

5.2 Clinical question 2: what is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B and PUVA in adult patients with MF-CTCL (stage IIB-IV) or adult MF-CTCL patients (regardless of stage) with patches or plaques in the head/neck regions or the genitals, who have had inadequate effect to at least one optimised topical treatment?

In the DMC protocol on chlormethine gel, the expert committee has outlined a clinical question where chlormethine 0.02% gel is assessed in MF-CTCL patients with stage IIB-IV disease or MF-CTCL patients regardless of stage with patches or plaques in the head/neck regions or the genitals who have experienced an inadequate response to at least one optimised topical treatment. The systematic literature did not identify any studies assessing the outlined outcomes in the requested populations. Therefore, we are not able to present any data or comparative analyses to demonstrate the value of chlormethine 0.02% gel in these populations.

6. Other considerations

In the following, we have described the real-world treatment landscape and challenges of MF-CTCL, to give the DMC a better understanding of the disease and elaborated on subjects we hope the DMC will consider when evaluating chlormethine gel for treating MF-CTCL patients.

Mycosis fungoides (MF) represents the majority of the primary cutaneous T-cell lymphomas (CTCL). Most patients have early stage MF with localised patches and plaques and a good survival outcome, but many progresses to late stages with tumors, erythroderma, and systemic involvement. Disease management is based on stage directed treatment with early stage MF (IA-IIA) patients primarily being treated with SDTs including topical corticosteroids, chlormethine, retinoids, phototherapy, and radiotherapy (localised or total skin electron beam therapy).
Advanced stages (IIB-IVB) or refractory MF often requires systemic treatments which may be used in combination with SDTs. These are primarily used as a palliative approach, aiming to provide symptomatic relief. (14)

MF-CTCL could be considered a chronic disease for a majority of patients in the initial stages of the disease and involves physicians and patients having to manage the disease over a very long period of time. Patients go through periods of remission and phases of relapse of the disease and physicians must manage a variety of treatments to respond to the loss of efficacy, the occurrence of undesirable side effects, patient choices and finally sometimes the progression of the disease to more advanced stages. Each patient is unique, and the course of the disease requires clinicians to make individualised therapeutic choices. Thus, it is extremely complicated to classify these different therapeutic options because they are generally used, or useful during the initial phases of the disease (stages I to IIB). Physicians have to consider the efficacy and time to relapse of treatments, side effects, the sequencing of treatments over time relative to each other (in connection with the course of the disease), contraindications of some treatments (e.g. number maximum of cycles of phototherapy), the possibility of combining certain treatments (in connection with the course of the disease), the specific needs of the physicians in connection with the specificities of the patient (e.g. localisation of skin lesions) and the patient's wishes. (15,16)

No direct comparative studies exist where the efficacy of phototherapy (BB-UVB, NB-UVB, UVA1, PUVA, BB-UVA, and the excimer laser), topical steroids or chlormethine gel is compared. These treatment options are complementary and may be sequenced or often combined, but do not replace each other. It is important to consider that these patients, particularly in early stages, have a close to normal life expectancy.

Topical corticosteroids
Many patients initially receive topical steroids since, before being diagnosed, this pathology manifests itself in skin damage that physicians and more particularly dermatologists are used to treat with corticosteroids. Once the diagnosis is made, corticosteroids (class 1 to 4) always play a role in the management of skin lesions given their anti-inflammatory properties and may well be used concomitantly with other SDTs. Topical steroids may be effective in treating lesions, but the duration of effect is very short. The efficacy of high potency corticosteroids compared to less potent steroids has only been investigated in one controlled study and do not induce a lasting CR or PR in treating patients' skin lesions (17). Topical steroids cause a variety of adverse events, which make their long-lasting use difficult for a patient. Skin atrophy is an adverse event of corticosteroids manifesting as bruises, particularly those in advanced stage disease (18). Physicians may recommend against topical steroids in treating skin lesions and patients often reject them. In certain areas of the body, the application of topical corticosteroids should therefore be done with caution (areas with thin skin e.g. the face, the genitals etc.) and its use over a long period of time is not encouraged, which was supported by the Danish clinical expert Dr. Iversen. Side effects following the cutaneous penetration of corticosteroids cannot be excluded (19). Percutaneous absorption of topical steroids involves passage

of the drug through the epidermis, dermis, and into the circulation. Topical medicines have poor total absorption and a very slow rate of absorption and topical steroids are no exception. The stratum corneum acts as the rate-limiting barrier to percutaneous drug absorption. Due to varying thickness of this layer at different body parts, drug penetration also varies at different sites being highest through the mucous membrane and scrotal skin and least through palmo-plantar skin. Percutaneous toxicity of topical steroids is directly related to percutaneous absorption, so factors governing percutaneous absorption also influence systemic side effects. Some of these factors are:

- Age of the patient;
- Body site and area treated: Penetration of the drug correlates inversely with the thickness of the stratum corneum;
- Amount of topical steroid used: Absorption is directly proportional to the mass or concentration of topical steroid applied to the skin up to a critical point;
- Structure and Potency of the drug: with higher potency, the change of systemic side effects increases;
- Frequency of application: Repeated application increases the contact period and thus total absorption; and
- Duration of therapy.

Phototherapy

Phototherapy is well suited for vast lesion areas such as the trunk or extremities and can be combined with topical steroids and/or chlormethine gel in specific selected lesions, where phototherapy is not the appropriate choice. Phototherapy and chlormethine gel are generally considered to provide similar efficacy in treating patches and plaques as it relates to mSWAT and CAILS response. Estimates on the time to relapse with phototherapy in real-life practice vary, but highly experienced physicians generally estimate the following: Prof. Martine Bagot's (Head of Dermatology Department, Hôpital Saint Louis of Paris – France), who is one of the internationally most recognised experts in the management of MF-CTCL patients states that patients in clinical practice may relapse in a time window of one to six months. Dr. Iversen (Department of Dermatology, Aarhus University Hospital, Denmark) estimates for PUVA a time to relapse of six to 12 months and for UVB of four to eight months.

Phototherapy, particularly PUVA, may cause burns and is contraindicated in patients with tumours, which means that it is contraindicated in most patients with advanced disease given the risk of increased secondary malignancy with phototherapy. Generally, phototherapy use is limited in time since with increased exposure the risk of secondary malignancies increases. Phototherapy is not considered an appropriate choice in lesions in skin thin areas (e.g. face, genitals) due to the carcinogenicity risk. Also, its efficacy in folds may be limited given possible lesion accessibility challenges. Phototherapy is considered well suited to treat lesions of the head and neck area other than the face.

Chlormethine gel

As a bifunctional alkylating agent that inhibits rapidly proliferating cells, chlormethine gel has demonstrated clinical efficacy in improving the patches and plaques associated with MF-CTCL (1). This is in contrasts to other treatments for MF-CTCL, such as corticosteroids, that only alleviate the symptoms of the condition rather than targeting cancer cells specifically. Its efficacy in treating skin lesions has been well demonstrated in the largest, controlled prospective study in MF-CTCL, i.e. the pivotal Study 201 and has been confirmed in publications (6). Currently, there are no reliable data on chlormethine gel on the time to relapse. However, topical nitrogen mustard has been used historically in the treatment of MF-CTCL. Kim et al. 2003 present long-term data on topical mechlorethamine (i.e. chlormethine) and show a median time to relapse of 12 months based on a considerable cohort of 203 patients (20). A retrospective German study by Wehkamp et al, which was recently accepted for publication, provides further evidence of chlormethine gel's efficacy and safety in pre-treated MF-CTCL (21). The majority of the 18 IA to IIB patients had received more than 5 (8/18; 44.4%) or 2-4 (7/18; 38.9%) prior treatment lines, respectively, including 15/18 (88.2%)

patients who had received a systemic treatment line for MF. Only one patient had not been pre-treated before chlormethine gel was initiated. 37.5% achieved CR and 25% PR as a best response. Mean (median) mSWAT at treatment start was 5.1. The application frequency among these 18 patients was once daily in 38.9% of patients and 3 to 4 times a week in 61.1% of patients (21). While the company is aware of the limitations of a retrospective study with limited size, the above-mentioned data may further inform the clinical questions raised as to chlormethine gel's efficacy in pre-treated patients.

Corticosteroids do not induce a lasting CR or PR in treating patients' skin lesions. Since patients relapse fast and prolonged use of topical steroids is not recommended by leading physicians (see above), chlormethine gel represents a suitable topical option for recurrent or persisting lesions. Particularly, in localised lesions, usage of chlormethine gel is deemed to be more appropriate than exposing patients to increased carcinogenicity risk with phototherapy or to escalate treatment to systemic treatments such as oral bexarotene or pegylated interferon which may be burdensome for patients and more costly to the healthcare system (22,23). Also, access to PUVA is limited in Denmark as indicated by Dr. Iversen and travel/time requirements for patients may be very burdensome. Furthermore, access to phototherapy treatment centers during the COVID-19 pandemic may be difficult if photobiology units are closed or access is restricted (24).

Chlormethine gel can be well applied in the head/neck lesion area but may be irritant and shall be used with caution in genitals/folds lesions. In line with DMC's preferred place in therapy, i.e. patients who have had an insufficient effect in treating patches and plaques with a previous treatment, the Study 201 recruited patients who had been treated with a least one prior SDT (6). Even though data on specific lesion locations as requested by the DMC are not available since such clinical trials in a rare disease like MF-CTCL lack practical feasibility, Study 201 should provide robust evidence of chlormethine gel's efficacy and safety in DMC's preferred patient population for chlormethine gel. Treatment guidelines confirm chlormethine gel's place in therapy in both early stage and advanced stage disease. Table 18 provides a schematic representation of the recommendations/consensus/guidelines and the patients treated. Each recommendation published by scientific/medical societies has specific details and limitations to consider.

Table 18: MF-CTCL patient staging from guidelines/consensus and number of patients treated. Source:

Patient staging	IA	IB	IIA	IIB	III	IV
EORTC guidelines						
ESMO guidelines						
NCCN guidelines						
UK guidelines						

Chlormethine gel is a convenient home treatment for MF-CTCL skin lesions and a valuable treatment option as it does not require blood monitoring or hospital visits. Thus, it avoids the burdensome requirement of undergoing multiple phototherapy sessions in hospitals' photobiology units to which access in general (and specifically in COVID-19 pandemic times) are difficult. Considering the absence of evidence on systemic absorption, no systemic drug-drug interactions are expected when used concomitantly with other agents, as would occur with phototherapy in advanced stage patients who receive concomitant treatment with systemic therapy. No increased carcinogenicity risk has been shown unlike phototherapy (29).

In advanced patients chlormethine gel can be used in combination with systemic treatment when insufficient effect is observed on patch/plaques lesions. Its use in more advanced patients (IIB+ stages) suggests that it is an important therapeutic option for patients with MF skin lesions of all stages. In addition, since patients with advanced disease are co-treated with systemic therapies, no drug-drug interactions are expected due to the lack of systemic absorption1 of chlormethine gel. (30)

Treatment duration of chlormethine gel

The DMC has requested information in the duration treatment with chlormethine gel. No specific treatment duration is outlined for chlormethine gel and treatment should be continued until the patient experience disease progression, treatment-limiting toxicity, concomitant illness, or any change in health status that requires treatment discontinuation. Moreover, treatment discontinuation is generally expected if patients experience CR. In Study 201, the mean treatment duration and the median treatment duration were 39.3 and 51.7 weeks, respectively, as seen in Table 19. In 2014, a temporary use authorisation (ATU) was granted in France for the prescription of chlormethine 0.02% gel for MF-CTCL patients. 876 patients in France was prescribed chlormethine gel and 858 received at least one dose. Initially, only patients with early-stage MF-CTCL could be awarded an ATU for one, two, three or six months, after which response was measured and treatment could be continued on another ATU. At first, chlormethine gel was prescribed according to the criteria set out in Study 201, to only include patients with stage IA–IIA disease; the nominative cohort. Later on, the prescription criteria were expanded to allow for treatment of patients regardless of disease stage; forming the ATU cohort. The mean and median treatment duration observed in the ATU study were 15.68 weeks and 10.09 weeks, respectively (31).

Table 19: Treatment exposure (in weeks) in Study 201

Exposure in weeks	Chlormethine gel (n=128)
Mean (SD)	39.3 (19.34)
Median	51.7
IQR (Q1-Q3)	22.1-52.6
Range (min-max)	1-60
By range of weeks, n (%)	
0	0 (0.0)
>0-4	5 (3.9)
>4-8	14 (10.9)
>8-12	7 (5.5)
>12-16	2 (1.6)
>16-20	3 (2.3)
>20-24	2 (1.6)
>24-28	4 (3.1)
>28-32	3 (2.3)
>32-36	3 (2.3)

>36-40	0 (0.0)
>40-44	2 (1.6)
>44-48	2 (1.6)
>48	81 (63.3)

7. References

1. European Medicines Agenc. Summary of product characteristics: Ledaga [Internet]. European Medicines Agency; 2019 Last updated in [cited 2020 Nov 18]. Available from: https://www.ema.europa.eu/en/documents/product-information/ledaga-epar-product-information_en.pdf

2. Vonderheid EC. Topical mechlorethamine chemotherapy. Considerations on its use in mycosis fungoides. Int J Dermatol. 1984;

3. Beneton DD, Laribi K. Management of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL): focus on chlormethine gel. Cancer Manag Res. 2019;

4. Dronkert M, Kanaar R. Repair of DNA interstrand cross-links. Mutat Res. 2001;

5. Osawa T, Davies D. Mechanism of cell death resulting from DNA interstrand cross-linking in mammalian cells. Cell Death Dis. 2011;

6. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, et al. Topical Chemotherapy in Cutaneous T-cell Lymphoma: Positive Results of a Randomized, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02%, Gel in Mycosis Fungoides. JAMA Dermatol. 2013 Jan 1;149(1):25.

7. El Sayed H, Shalaby S, Abdel-Halim MRE. Efficacy of doxycycline in the treatment of early stages of mycosis fungoides: a randomized controlled trial. J Dermatol Treat. 2019 Sep;

8. Kim E, Geskin L. Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study. J Am Acad Dermatol. 2020;

9. Kim E, Geskin L. Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study. Abstr Eur J Cancer. 2019;

10. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Ledaga [Internet]. European Medicines Agency; 2016 Dec p. 76. Available from: https://www.ema.europa.eu/en/documents/assessment-report/ledaga-epar-public-assessment-report_en.pdf

11. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011 Jun 20;29(18):2598–607.

12. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin. 2012;

13. J. Kim E, Guitart J. The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. Am J Clin Dermatol [Internet]. 2021 Mar; Available from: https://pubmed.ncbi.nlm.nih.gov/33656660/

14. Lovgren M-L, Scarisbrick JJ. Update on skin directed therapies in mycosis fungoides. Chin Clin Oncol [Internet]. 2019 [cited 2021 Feb 23]; Available from: https://pubmed.ncbi.nlm.nih.gov/30525757/

15. Larocca C, Kupper T. Mycosis Fungoides and Sézary Syndrome: An Update. Hematol Oncol Clin North Am. 2019 Feb;

16. Jawed SI, Myskowski PL. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome) Part II. Prognosis, management, and future directions. J Am Acad Dermatol. 2014 Feb;70(2).

17. Zackheim HS, Kashani-Sabert M. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol. 1998 Aug;

18. Machet L, Jan V. Cutaneous alternariosis: role of corticosteroid-induced cutaneous fragility. Dermatology [Internet]. 1996 [cited 2021 Feb 23]; Available from: https://pubmed.ncbi.nlm.nih.gov/8993964/

19. Dhar S, Seth J, Parikh D. Systemic side-effects of topical corticosteroids. Indian J Dermatol. 2014;

20. Kim Y, Liu H, Mraz-Gernhard S. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003;

21. Wehkamp U. Management of chlormethine gel treatment in two German skin lymphoma centers (accepted for publicaton February 2021). J Ger Soc Dermatol. 2021 Feb;

22. European Medicines Agenc. Summary of product characteristics of bexarotene (Targretin). European Medicines Agency;

23. European Medicines Agenc. Summary of product characteristics: peginterferon alfa-2b (PEGINTRON) [Internet]. [cited 2021 Feb 22]. Available from: https://www.ema.europa.eu/en/documents/product-information/pegintron-epar-product-information_en.pdf

24. Papadavid E, Scarisbrick J. Management of primary cutaneous lymphoma patients during COVID-19 pandemic: EORTC CLTF guidelines. J Eur Acad Dermatol Venereol. 2020;34.

25. Trautinger F, Eder J, Assaf C. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2017;

26. Willemze R, Hodak E. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2018 Oct [cited 2021 Feb 22];29. Available from: https://www.annalsofoncology.org/article/S0923-7534(19)31693-X/fulltext

27. National Comprehensive Cancer Network (NCCN) [Internet]. [cited 2021 Feb 22]. Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf

28. Gilson D, Whittaker S. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol [Internet]. 2019 [cited 2021 Feb 22]; Available from: https://www.bad.org.uk/shared/get-file.ashx?id=6265&itemtype=document

29. Lindhal L. Secondary cancers, comorbidities and mortality associated with nitrogen mustard therapy in patients with mycosis fungoides: A 30-year population-based cohort study. Br J Dermatol [Internet]. 2014 Mar [cited 2021 Feb 22]; Available from: https://pubmed.ncbi.nlm.nih.gov/24024659/

30. Querfeld C, Geskin L. Lack of Systemic Absorption of Topical Mechlorethamine Gel in Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. J Invest Dermatol [Internet]. 2021 Jan; Available from: https://pubmed.ncbi.nlm.nih.gov/33347924/

31. Bagot M, Beylot-Barry M. Use of chlormethine (CL) gel in the treatment of mycosis fungoides (MF) from the French early access program. 2019; EADV.

32. ClinicalTrials.gov. Clinical Study Assessing Outcomes, Adverse Events, Treatment Patterns, and Quality of Life in Patients Diagnosed With Mycosis Fungoides Cutaneous T-cell Lymphoma (PROVe) [Internet]. [cited 2020 Nov 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT02296164?term=NCT02296164&draw=2&rank=1

33. Sayed HE. Efficacy of Doxycycline in the Treatment of Early Stages of Mycosis Fungoides: A Randomized Controlled Trial [Internet]. clinicaltrials.gov; 2018 Aug [cited 2020 Nov 16]. Report No.: NCT03454945. Available from: https://clinicaltrials.gov/ct2/show/NCT03454945

8. Appendices

8.1 Literature search

In the following, we present the inclusion and exclusion criteria used in the systematic literature search (in Table 19), the search terms used in PubMed and the Cochrane library with identified hits (in Table 20 and Table 21), and a list of the excluded references with an explanation as to why they were excluded (in Table 22).

Table 20: Inclusion and exclusion criteria used in the systematic literature search.

Inclusion criteria	**Population**: 1) Adult patients with early stages of MF-CTCL (I-IIA) who have inadequate effect of at least one previous optimised topical treatment. 2) Adult patients with MF-CTCL stages IIB-IV or regardless of stage, patients who have patches or plaques in the head/neck regions or the genitals who have experienced inadequate effect of at least one previous optimised topical treatment. **Intervention(s):** Chlormethine gel (0.02%) applied once daily. **Comparator(s):** 1) Topical corticosteroids, 2) Narrow-band UV-B, 3) 8-methoxypsoralen + UV-A (PUVA) **Outcomes:** Reduction of skin symptoms (CR or PR) measured with mSWAT, quality of life measured with the Skindex-29 questionnaire, median duration of response and adverse events (grade 3 or grade 4 and serious adverse events). **Study design:** None outlined due to limited available evidence. **Language restrictions:** Only Danish or English**.** **Other search limits or restrictions applied:** None.
Exclusion criteria	**Population:** Other types of MF-CTCL, e.g. hypopigmented MF-CTCL and children, adolescence, and geriatric populations. CTCL populations without specification of MF and references where it was not specified if patients had previously received topical treatment. **Intervention(s):** Studies including nitrogen mustard, mechlorethamine and chlormethine of other concentrations. **Comparator(s):** Studies where the comparators have been studied in combination with other treatments or did not follow the treatment-regimen outlined in the DMC protocol. **Outcomes:** All other outcomes not included in the DMC protocol on chlormethine. **Settings (if applicable):** NA **Study design:** Due to the limited amount of relevant evidence, we did not outline any exclusion criteria regarding study design. **Language restrictions:** Other languages than Danish and English. **Other search limits or restrictions applied:** None.

Table 21: Search terms and hits in PubMed (05 November 2020).

#	Search terms	Comment	Hits
1	Lymphoma, T-Cell, Cutaneous[majr]	Terms for the indication	8,409
2	(MF-type[tiab] and CTCL[ti]) OR (cutaneous[ti] AND t-Cell[ti] AND lymphom*[ti]) OR (mycosis[ti] AND fungoides[ti])		6,910
3	#1 OR #2		9,741
4	Mechlorethamine[mh]	Terms for intervention and comparators	5,565
5	mechlorethamin*[tiab] OR chlormethin*[tiab] OR Ledaga[tiab] OR Nitrogen mustard[tiab] OR Chlorethazin*[tiab] OR Mustine[tiab]		4,502
6	(Administration, Cutaneous[mh] OR Administration, Topical[mh]) AND (Adrenal Cortex Hormones[mh] OR Steroids[mh])		16,766
7	corticosteroid*[tiab] OR hydrocortison*[tiab] OR cobadex[tiab] OR dioderm[tiab] OR efcortelan[tiab] OR hydrocortisyl[tiab] OR mildison[tiab] OR alphaderm[tiab] OR calmurid[tiab] OR locoid[tiab] OR alclometason*[tiab] OR modrasone[tiab] OR beclomethason*[tiab] OR beclometason*[tiab] OR propaderm[tiab] OR betamethason*[tiab] OR betametason*[tiab] OR betacap[tiab] OR betnovate[tiab] OR diprosone[tiab] OR diprosalic[tiab] OR bettamousse[tiab] OR clobetasol*[tiab] OR dermovate[tiab] OR clobetason*[tiab] OR eumovate[tiab] OR trimovate[tiab] OR desoxymethason*[tiab] OR desoximetason*[tiab] OR stiedex[tiab] OR diflucortolon*[tiab] OR nerison*[tiab] OR fluocinolon*[tiab] OR synalar[tiab] OR fluocinonid*[tiab] OR metosyn[tiab] OR fluocortolon*[tiab] OR ultralanum[tiab] OR flurandrenolon*[tiab] OR fludroxycortid*[tiab] OR haelan[tiab] OR fluticason*[tiab] OR cutivate[tiab] OR halcinonid*[tiab] OR halciderm[tiab] OR mometason*[tiab] OR elocon[tiab] OR triamcinolon*[tiab] OR adcortyl[tiab] OR aureocort[tiab] OR tri-adcortyl[tiab]		137,854
8	Ultraviolet Therapy[majr]		6,013
9	PUVA[tiab] OR ultraviolet[tiab] OR (psoralen[tiab] AND (UVA[tiab] OR ultraviolet-A[tiab])) OR UVB[tiab]		88,305
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9		244,469
11	#3 AND #10	Combination of indication, intervention, and comparator	1,080
12	Animals[mh] NOT Humans [mh]	Exclusion of irrelevant studies and publication types	4,753,314
13	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]		1,543,440
14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]		6,605,697
15	#12 OR #13 OR #14		11,368,846

16	**#11 NOT #15**	**Final search**	**528**

Table 22: Search terms and hits in CENTRAL (05 November 2020).

#	Search terms	Comment	Hits
1	[mh "Lymphoma, T-Cell, Cutaneous"]	Terms for the indication	95
2	("mycosis fungoides" or "cutaneous T cell lymphoma"):kw		184
3	MF-type:ti,ab and CTCL:ti		2
4	(cutaneous near "t cell" near lymphom*):ti OR (mycosis near fungoides):ti		233
5	#1 or #2 or #3 or #4		305
6	(mechlorethamine or chlormethine):kw	Terms for intervention and comparators	270
7	(mechlorethamin* or chlormethin* or "nitrogen mustard" or chlorethazin* or Mustine):ti,ab		204
8	[mh "Adrenal Cortex Hormones"]		14,390
9	[mh Steroids]		58,630
10	glucocorticoid:kw		926
11	(corticosteroid* or hydrocortison* or cobadex or dioderm or efcortelan or hydrocortisyl or mildison or alphaderm or calmurid or locoid or alclometason or modrasone or beclomethason* or beclometason* or propaderm or betamethason* or betametason* or betacap or betnovate or diprosone or diprosalic or bettamousse or clobetasol* or dermovate or clobetason* or eumovate or trimovate or desoxymethason* or desoximetason* or stiedex or diflucortolon* or nerison* or fluocinolon* or synalar or fluocinonid* or metosyn or fluocortolon* or ultralanum or flurandrenolon* or fludroxycortid* or haelan or fluticason* or cutivate or halcinonid* or halciderm or mometason* or elocon or triamcinolon* or adcortyl or aureocort or tri-adcortyl):ti,ab,kw		40,076
12	("ultraviolet therapy" or "ultraviolet phototherapy" or puva or "puva therapy"):kw		742
13	(PUVA or ultraviolet or (psoralen AND (UVA or "ultraviolet A")) OR UVB):ti,ab		22,950
14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13		88,215
15	#5 and #14	Combination of indication, intervention and comparator	76
16	("conference abstract" or review):pt	Exclusion of irrelevant studies and publication types	180,293
17	NCT*:au		198,147
18	("clinicaltrial gov" or trialsearch):so		143,157
19	(meeting or abstract or review):ti		155,21
20	#16 or #17 or #18 or #19		532,863

21	#15 not #20	**Final search (limit to trials)**	**44**

Table 23: List of excluded references after full-text assessment and an explanation as to why the reference was excluded.

Reference	Potentially relevant for clinical question	Reason for exclusion
Nikolaou et al. 2018: Phototherapy as a first-line treatment for early-stage mycosis fungoides: The results of a large retrospective analysis.	1	Did not match the patient population in the protocol: An exclusion criterion in the publication was if patients had previously been treated with a topical treatment.
Ahmad et al. 2007: Narrowband UVB and PUVA in the treatment of mycosis fungoides: a retrospective study.	1	The article does not state how treatment response is measured, and AEs are not reported as grade 3 or 4.
Diederen et al. 2003: Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study.	1	The article does not state how treatment response is measured, and AEs are not reported as grade 3 or 4.
Ponte et al. 2010: Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides.	1	The article does not state how treatment response is measured, and AEs are not reported as grade 3 or 4.
Coronel-Pérez et al. 2007: Narrow band UVB therapy in early stage mycosis fungoides. A study of 23 patients.	1	Not clear if patient population matches with the protocol, as it states that UVB is given as first-line treatment. Furthermore, it is not stated how treatment response is measured. AEs were not reported as grade 3 or 4.
Brazzelli et al. 2007: Narrow-band ultraviolet therapy in early-stage mycosis fungoides: study on 20 patients.	1	Not clear if patients have had an inadequate response to previous topical treatment, and it is not stated how treatment response is measured. AEs were not reported as grade 3 or 4.
Zackheim et al. 1998: Topical corticosteroids for mycosis fungoides. Experience in 79 patients.	1	Patients had previously received topical treatment, but response was not measured with the mSWAT and AEs was not reported as grade 3 or 4.
Yan Y et al. 2015: Efficacy and safety of topical PUVA treatment for refractory lesions of mycosis fungoides.	1	Not possible to identify and retrieve full-text article.

Boztepe et al. 2005: Narrowband ultraviolet B phototherapy to clear and maintain clearance in patients with mycosis fungoides.	1	Not stated how response is measured and AEs were not reported as grade 3 or 4.
Gókdemir et al. 2006: Narrowband UVB phototherapy for early-stage mycosis fungoides: evaluation of clinical and histopathological changes.	1	No relevant outcomes.
Whittaker et al. 2012: Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056).	1	Mixed population of treatment-naïve patients and patients who have previously received treatment. Not stated how response was measured.
Kartan et al. 2020: Response to Topical Corticosteroid Monotherapy in Mycosis Fungoides.	1	Excluded because patients who previously received topical treatment or were currently receiving additional treatment for MF, including other skin-directed treatments, were excluded. Furthermore, the dose-regimen of corticosteroids does not match the one in the protocol.
Roupe et al. 1996: PUVA in early mycosis fungoides may give long-term remission and delay extracutaneous spread.	1	No relevant outcomes.
Querfeld et al. 2005: Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy.	1	Patients are topical treatment-experienced, but it is not reported how response is measured and AEs were not reported as grade 3 or 4.
Pavlotsky et al. 2006: UVB in the management of early stage mycosis fungoides.	1	Not stated if they are previously treated with topical treatments or how response was measured.
Elcin et al. 2014: Long-term follow-up of early mycosis fungoides patients treated with narrowband ultraviolet B phototherapy.	1	Not stated if patients had previously had an inadequate response to topical treatment and how response was measured.
Xiao et al. 2008: Narrow-band ultraviolet B phototherapy for early stage mycosis fungoides	1	Full text only available in Chinese.
Molin et al. 1981: Photochemotherapy (PUVA) in the tumour stage of mycosis fungoides: a report from the Scandinavian Mycosis Fungoides Study Group.	1	Not able to identify and retrieve full-text article.

Almohideb et al. 2017: Bath Psoralen-ultraviolet A and Narrowband Ultraviolet B Phototherapy as Initial Therapy for Early-stage Mycosis Fungoides: A retrospective cohort of 267 Cases at the University of Toronto.	1	Patients do not match the outlined patient population: Those who received any skin-directed therapy before initiating either narrowband UVB or PUVA were excluded from the study.
Anadolu et al. 2005: Mycosis fungoides and Sezary syndrome: therapeutic approach and outcome in 113 patients.	1	Patients had previously received topical treatment (assume they match the patient population in the protocol) but none of the outcomes were relevant.
Hernández et al. 2014: Treatment of stage Ia and Ib mycosis fungoides with psoralen UVA monotherapy: an observational study in tertiary hospitals in the Canary Islands.	1	None of the outcomes in the study were relevant, and only 22 out of 31 patients had previously been treated with topical treatment (we assume not all patients match the outlined patient population).
Geller et al. 2020: Topical clobetasol propionate treatment and cutaneous adverse effects in patients with early-stage mycosis fungoides: an observational study.	1	Approximately 50% of patients had previously been treated with topical treatment. However, the reported outcomes were not relevant.
Wackernagel et al. 2006: Efficacy of 8-methoxypsoralen vs. 5-methoxypsoralen plus ultraviolet A therapy in patients with mycosis fungoides.	1	Provides no information about if patients had previously experienced an inadequate response to topical treatment.
Polariska et al. 2017: High-frequency ultrasonography in objective evaluation of the efficacy of PUVA and UVA 1 phototherapy in mycosis fungoides.	1	Measures treatment response with mSWAT but does not state if patients have previously had inadequate response to topical treatment.
Abel et al. 1987: PUVA treatment of erythrodermic and plaque-type mycosis fungoides. Ten-year follow-up study.	1	Not able to identify and retrieve full-text article
Dereure et al. 2009: Treatment of early stages of mycosis fungoides with narrowband ultraviolet B. A clinical, histological, and molecular evaluation of results.	1	No relevant outcomes.
Jang et al. 2011: Narrowband ultraviolet B phototherapy of early stage mycosis fungoides in Korean patients.	1	Asian patients and no relevant outcomes.

Herrmann et al. 1995: Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up.	1	None of the outcomes reported were relevant, and not all patients had previously received topical treatment.
Thomsen et al. 1989: Retinoids plus PUVA (RePUVA) and PUVA in mycosis fungoides, plaque stage. A report from the Scandinavian Mycosis Fungoides Group.	1	Not able to identify and retrieve full-text article.
Abel et al. 1981: PUVA treatment of erythrodermic and plaque type mycosis fungoides.	1	No relevant outcomes.
Pattamadilok et al. 2020: A retrospective, descriptive study of patients with Mycosis fungoides treated by phototherapy (oral PUVA, NB-UVB) with a twice-weekly regimen at the Institute of Dermatology, Bangkok, Thailand, with an experiential timeline of 13 years.	1	Does not state if patients have previously received topical treatment, and none of the outcomes are relevant.
Hofer et al. 1999: Narrowband (311-nm) UV-B therapy for small plaque parapsoriasis and early-stage mycosis fungoides.	1	No relevant outcomes.
Molin et al. 1980: Aspects of the treatment of mycosis fungoides. A report from the Scandinavian Mycosis Fungoides Study Group.	1	Not able to identify and retrieve full-text article.
Du Viver et al. 1981: Nitrogen mustard and PUVA therapy of mycosis fungoides.	1	Not able to identify and retrieve full-text article.
Konrad et al. 1978: Photochemotherapy in mycosis fungoides.	1	Not able to identify and retrieve full-text article.
Marschalkó et al. 2001: Interferon-alpha and PUVA therapy for mycosis fungoides.	1	Not able to identify and retrieve full-text article.
Piccinno et al. 1989: Results of photochemotherapy in a series of 47 patients with mycosis fungoides.	1	Not able to identify and retrieve full-text article.
Rotstein et al. 1980: The treatment of mycosis fungoides with PUVA.	1	Not able to identify and retrieve full-text article.
Hönigsmann et al. 1987: Treatment of mycosis fungoides with PUVA.	1	Not able to identify and retrieve full-text article.
Faber et al. 1968: Treatment of mycosis fungoides with various strengths of fluocinolone acetonide cream.	1	Not able to identify and retrieve full-text article.

Whittaker et al. 2003: Phase III Randomized Study of Ultraviolet A Light Therapy With Methoxsalen (PUVA) With or Without Bexarotene in Patients With Mycosis Fungoides.	1	Not able to identify and retrieve full-text article.
Neering et al. 1972: Treatment of localized skin lesions with betamethasone 17-valerate and triamcinolone acetonide in alcoholic solution under occlusive dressing. A double-blind comparative study.	1	Not able to identify and retrieve full-text article.
Vieyra-Garcia et al. 2019: Evaluation of Low-Dose, Low-Frequency Oral Psoralen–UV-A Treatment With or Without Maintenance on Early-Stage Mycosis Fungoides A Randomized Clinical Trial.	1	Patients do not match the outlined population as only half have previously received topical treatment.

8.2 Main characteristics of included studies

In the following, we present the main characteristics of the studies included in the assessment of chlormethine 0.02% gel and outlined comparators. Table 23 presents the main characteristics of Study 201 and is informed by the EPAR on chlormethine 0.02% gel, the CSR on Study 201, and the publication by Lessin et al. 2013 (6,10). Table 24 presents the main characteristics of the PROVe study and is informed by the research letter and abstract by Kim et al. 2020 and Kim et al. 2019, respectively, together with trial information from www.clinicaltrials.gov. Table 25 presents the main characteristics of the study by El Sayed et al. 2019 and is informed by the publication (7).

Table 24: Main characteristics of Study 201

Trial name	Study 201
NCT number	NCT00168064
Objective	Primary objective: Compare chlormethine 0.02% gel with chlormethine 0.02% ointment in previously treated patients with MF-CTCL stage IA-IIA. Secondary objective: To evaluate the tolerability and safety of topical chlormethine 0.02% gel and chlormethine 0.02% ointment.
Publications – title, author, journal, year	Title: Topical Chemotherapy in Cutaneous T-cell Lymphoma. Positive Results of a Randomised, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02% Gel in Mycosis Fungoides Author: Lessin et al. 2013 Journal and year: Jama Dermatol. Vol. 149, January 2013
Study type and design	Phase II, multicentre, randomised (1:1), observer-blinded, active-controlled trial. The trial is completed and published. The Master List of Randomisation Numbers with the corresponding study drug assignments were sent to the site pharmacist. It was the responsibility of the site pharmacist to order and provide the correct study drug using the master list. Eligible patients were stratified into two groups by MF stage (IA vs. IB, IIA). Blinding (masking): The study site personnel not involved with patient assessment

	were not blinded. Investigators and any other individuals involved with patient assessment were blinded to the assigned treatment.
Follow-up time	The study period in Study 201 was 12 months. An off-study safety period of 12 months after Study 201 was conducted (study 202).
Population (inclusion and exclusion criteria)	MF-CTCL patients with persistent or recurrent stage IA, IB or IIA disease. Inclusion criteria (from clinicaltrials.gov): • Patients with stage IA, IB or IIA MF-CTCL confirmed with skin biopsy • No history of progression beyond stage IIA • Received at least one prior skin-directed treatment for MF-CTCL (e.g. PUVA, topical steroids) • Histological variants, e.g. folliculotropic/syringotropic MF-CTCL and large cell transformation (LCT) • Laboratory values within normal range and otherwise healthy Exclusion criteria (from clinicaltrials.gov): • Newly diagnosed with no prior treatment • Prior treatment with topical chlormethine within the last two years or topical carmustine • Use of topical or systemic therapies (including corticosteroids) for MF-CTCL within four weeks of study entry • Diagnosis of MF-CTCL stage IIB-IV • History of a higher T score than T2 and a higher N score than N1 in the TNMB classification system • Received radiation therapy within 1 year of study start • Individuals who are pregnant, nursing or with childbearing potential who did not use an effective contraception method • Serious known concurrent medical illness or infection which could present a safety risk or prevent compliance with the treatment program • No concurrent therapies (especially topical corticosteroids) were permitted among patients during the present trial, and no additional skin-directed or systemic therapies were used in the case of unresponsive or progressive disease.
Intervention	Chlormethine 0.02% gel (N=130) applied with a thin layer once daily to affected lesions or total skin surface, depending on BSA coverage. If new lesions appeared in untreated areas, patients were switched from lesion treatment to whole-body or regional treatment. Patients received treatment for 12 months. Treatment could be stopped due to progression, treatment-limiting toxicity, concomitant illness, or other health issues that necessitated discontinuation.

Baseline characteristics	**Characteristic**	**Chlormethine gel (N=130)**	**Chlormethine ointment (N=130)**
	Gender		
	Male – no. (%)	77 (60)	77 (59)
	Female – no. (%)	53 (40)	53 (41)
	Race		
	Caucasian – no. (%)	97 (75)	96 (74)
	Afro-American – no. (%)	16 (12)	19 (15)
	Other – no. (%)	17 (13)	15 (11)
	Age		
	<18 years – no. (%)	0 (0)	1 (1)
	18–64 years – no. (%)	93 (72)	86 (66)
	65–74 years – no. (%)	29 (22)	33 (25)
	≥75 years – no. (%)	8 (6)	10 (8)
	Prior MF Therapies		
	Topical Corticosteroids – no. (%)	112 (86)	113 (87)
	Phototherapy – no. (%)	50 (39)	53 (41)
	Bexarotene (topical & oral) – no. (%)	23 (18)	23 (18)
	Topical NM (>2yrs from study) – no. (%)	16 (12)	13 (10)
	Interferons – no. (%)	3 (2)	5 (4)
	Methotrexate – no. (%)	3 (2)	3 (2)
	Radiation (local & total skin) – no. (%)	3 (2)	2 (2)
	Other* – no. (%)	14 (11)	34 (26)
	MF Stage		

	Stage IA – no. (%)	76 (59)	65 (50)
	Stage IB – no. (%)	52 (40)	63 (49)
	Stage IIA – no. (%)	2 (1)	2 (1)

*"Other" includes primarily emollients, anti-bacterials, anti-fungals, and retinoids other than bexarotene.

Primary and secondary endpoints

The primary endpoint:

- Response rate (CR or PR) measured with CAILS, defined as a ≥50% improvement from the CAILS score at baseline. Outcomes and explanations are listed in the table below.

The secondary endpoints:

- mSWAT response rate with ≥50% improvement from baseline
- Time to confirmed CAILS response
- Duration of CAILS response
- Time to progression based on CAILS score
- Extent of cutaneous disease measured as percentage change in BSA involvement

Outcome	Definition/explanation
Primary endpoints	
Confirmed response	Any response with a duration of ≥28 days.
Complete response	No evidence of disease (100% improvement from baseline score) confirmed at next visit ≥28 days later.
Partial response	Partial clearance of disease (≥50% improvement from baseline score) confirmed at next visit ≥28 days later.
Stable disease (SD)	Disease has not changed from baseline (<50% improvement or <25% increase from baseline).
Disease progression (PD)	Disease has worsened since baseline (≥25% increase from baseline score).
Secondary endpoints	
Duration of confirmed CAILS response	Time from first appearance of confirmed response (CR or PR) to first assessment where the response was no longer

		apparent (SD and PD subsequently documented).
	Time to progression based on CAILS	Time from baseline to PD.
	Time to confirmed CAILS response	Time from baseline to the first confirmed CAILS response (CR or PR).
	Extent of cutaneous disease	Change from baseline in the total percentage of the BSA component of the mSWAT score calculation.

Method of analysis

<u>The primary efficacy variable</u>

The primary efficacy variable was the indication of a complete or partial response determined by CAILS within up to 12 months of study drug application by two or more consecutive observations over at least four weeks. Up to a maximum of five MF lesions was designated as index lesions. If the patient had five or fewer MF lesions, then all MF lesions was designated as index lesions. If the patient had more than five MF lesions, then five lesions that were representative of the patient's overall cutaneous disease were designated as index lesions. A Composite Assessment of Index Lesion Disease Severity was generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, and area. Patients within the 12-month period were categorised as showing complete response (which includes complete clinical response) or partial response. The following assessments of response to therapy were derived from standardised conventions of reporting responses to cancer treatments:

- Complete Response (CR): No evidence of disease; 100% improvement. A Composite Assessment of Index Lesion Disease Severity of 0.
- Partial Response (PR): Partial but incomplete clearance (≥50%); evidence of disease remains. Final Composite Assessment of Index Lesion Disease Severity score of ≥50% reduction from baseline score.
- Stable Disease (SD): Disease has not changed from baseline condition. A final Composite Assessment of Index Lesion Disease Severity of <50% reduction from baseline score.
- Progressive disease (PD): Disease is worse than at baseline evaluation by a Composite Assessment of Index Lesion Disease Severity of ≥25% increase from baseline.

<u>SWAT Score</u>

The primary efficacy variable was the indication of a complete or partial response determined by the SWAT score within up to 12 months of study drug application by two or more consecutive observations over at least four weeks. Patients within the 12-month period were categorised as showing complete response (which includes complete clinical response) or partial response. The following assessments of response to therapy are derived from standardised conventions of reporting responses to cancer treatments:

- Complete Response (CR): No evidence of disease; 100% improvement. A SWAT score of 0.

- Partial Response (PR): Partial but incomplete clearance (≥50%); evidence of disease remains. Final SWAT score of ≥50% reduction from baseline scores.
- Stable Disease (SD): Disease has not changed from baseline condition. A final SWAT score of <50% reduction from baseline score.
- Progressive Disease (PD): Disease is worse than at baseline evaluation by a SWAT score of ≥25% increase from baseline.

If a patient did not have a response, the SWAT score at the final available visit was used to determine by comparison with the patient baseline SWAT score the categorisation of stable or progressive disease. Patients with no SWAT score post-baseline was recorded as unevaluable. The number and percentage of patients within each of these categories was summarised. The analysis was performed to compare the proportion with complete or partial response between the two treatment groups. The analysis was performed in both the evaluable patient and ITT populations.

Extent of Cutaneous Disease

The total percentage body surface area component of the SWAT score calculation will be used as a measure of the overall extent of cutaneous disease. Changes from baseline to the final assessment in the percentage body surface area involvement was compared between the two treatment groups using the subject's initial value as covariate.

Time to response

The time to response for a given patient is defined as the time interval from the first day ointment was applied to the time of the first observation when the patient meets the criteria for CR or PR by the assessment of CAILS. For CR or PR this is the date of the evaluation at least 28 days after the first assessment of CR or PR which also shows a similar response sustained for at least that period with no intervening assessments indicating otherwise. The time to response, as assessed by the CAILS comparison with baseline, was treated as a quantitative variable and summarised accordingly with the number of patients responding in the ITT population and efficacy evaluable populations. Kaplan-Meier estimates of proportions of patients responding (complete or partial) within the intent to treat and efficacy evaluable populations for each planned time point in the study was shown. Patients not showing CR or PR sustained for at least 28 days was included in the analysis as censored observations at the time of their last assessment. The difference in time to response between the two treatment groups was assessed using log rank test and a 95% confidence interval of the difference in the Kaplan-Meier estimates of the proportion of patients responding at 12 months.

Response duration

For those patients who show a response (complete or partial) by assessment of the CAILS, the duration of the response was calculated as the time from the first appearance of the response to the first assessment where the response was no longer apparent. When the final assessment still showed a response, the time was taken to that response and the value censored to the right (i.e. recorded as greater than that duration). When multiple periods of response were indicated for a given patient, the maximum uncensored period was used in the analysis. Kaplan-Meier estimates of the proportion of patients still responding (complete or partial) was estimated at 28-day intervals. The difference in duration of response between the two treatment groups was assessed using log-rank test and a 95% confidence interval of the difference in the Kaplan-Meier estimates of the proportion of patients responding at 16 weeks.

	Time to progression The time to progression for each patient was calculated from the first day the ointment was applied to the date the first disease progression occurred (25% or greater increase in CAILS from that recorded at baseline). When the patient had no disease progression, the date of the last assessed CAILS was used and the value included in the analysis as a right censored value. If the patient had no CAILS after baseline, the patient had the duration recorded as 0 and the value considered right censored. Kaplan-Meier estimates of time to progression are presented for each planned time point in the study up to and including 12 months. The difference in time to progression between the two treatment groups was assessed using log-rank test and a 95% confidence interval of the difference in the Kaplan-Meier estimates of the proportion of patients with progression-free survival at 12 months in the two treatment groups. Adverse events AEs were coded according to Medical Dictionary for Regulatory Activities. They were classified into pre-defined standard categories according to chronological criteria. treatment-emergent AEs (TEAEs) are AEs that occurred for the first time or, if present before that, worsened during an exposure to study drug up to 30 days after the last administration of the study medication. An AE that started before starting study medication and which led to permanent study drug discontinuation was considered as treatment-emergent. Non-TEAEs are AEs that occurred before the first study drug or after 30 days following the last administration of study medication. Non-TEAEs were only listed. All summary tables of AEs by primary system organ class and preferred term were in decreasing order of system organ class frequency and decreasing order of preferred term frequency within the system organ class. The frequency was based on the overall frequency in both treatment groups. In cases of equal frequency regarding system organ class (or preferred term), alphabetical order was used. Treatment-limiting AEs were defined as grade 3 or 4 local dermal irritation (on a 4-point scale per protocol and by the National Cancer Institute Common Toxicity Criteria of Adverse Events) that did not resolve to grade 2 or lower within two weeks off the study drug. Grade 3 or 4 local dermal irritation associated with a positive patch was considered allergic contact dermatitis; other manifestations were considered irritant contact dermatitis. For grade 3 or 4 local dermal irritation, treatment frequency was suspended or reduced for up to a maximum of four weeks and was resumed after irritation improved to grade 2 or lower. Therapy for skin irritation included topical emollients and systemic antihistamines, but the use of topical or systemic corticosteroids was prohibited. Patients with positive–patch test results (allergic contact dermatitis) associated with grade 3 or 4 reactions were withdrawn from the study. Patients were evaluated for the development of squamous cell carcinomas of the skin for an additional 12 months after treatment (6).
Subgroup analyses	Post-hoc subgroup analyses (time to response and trend analyses) stratified by disease stage and conducted on efficacy data for the ITT and efficacy evaluation (EE) populations from Study 201. In the post-hoc analysis for the ITT population, chlormethine gel daily consumption was measured for the full cohort and in subgroups by stage and BSA. The objective was to assess the degree of heterogeneity by treatment separately in each subgroup as fixed effects. The response variable used in generalised linear models was the proportion of CR + very good partial response (VGPR) + PR at the final visit.

Table 25: Main characteristics of the PROVe study

Trial name	PROVe
NCT number	NCT02296164
Objective	To follow patients who receive treatment with chlormethine gel (Valchlor, equivalent to chlormethine 0.02% hydrochloride (HCl)) and assess the efficacy and QoL in these patients in a real-world setting.
Publications – title, author, journal, year	An abstract and a research letter have been published. The abstract: Title: Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study Author: Kim et al. 2019 Journal and year: European journal of cancer 2019 The research letter: Title: Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study Author: Kim et al. 2020 Journal and year: J Am. Acad. Dermatol. 2020
Study type and design	A multi-centre, prospective, observational, US-based drug study. All consecutive MF-CTCL patients being treated with Valchlor was invited to enrol in this study. Patients went through a clinical assessment and received standard medical care, as determined by the patients' physician, in the real-world setting. There were no specific or mandated clinical assessments performed, except for protocol-required completion of questionnaires for symptoms and QoL. Patients were followed prospectively for a maximum of two years.
Follow-up time	Maximum follow-up was two years.
Population (inclusion and exclusion criteria)	Inclusion criteria (from clinicaltrials.gov (32)): • All adult patients (≥ 18 years of age) diagnosed with MF-CTCL and being treated with Valchlor. This includes patients newly initiating Valchlor or patients continuing treatment with Valchlor: ◦ Patients newly initiating Valchlor are patients who have their first office visit after having initiated Valchlor. ◦ Patients continuing treatment with Valchlor includes patients who are actively taking Valchlor on the day of enrolment. • Signed patient-informed consent. Exclusion criteria: • None
Intervention	Valchlor

Baseline characteristics

From the research letter by Kim et al. 2020:

Characteristics*	Results (N=298)		
	At diagnosis	**Mechlorethamine gel initiation**	**PROVe enrolment**
Age (in years)	57.0 (13.0, 88.0)	NC	62.0 (21.0, 90.0)
Male		179 (60.1)	
Race/ethnicity			
White		203 (68.1)	
African American		45 (15.1)	
Hispanic or Latino		29 (9.7)	
Asian		11 (3.7)	
Native Hawaiian/other Pacific Islander		2 (0.7)	
Unknown or ≥2 races/ethnicities		8 (2.7)	
Duration of MF-CTCL, y	NC	2.3 (0.0, 48.2)	2.9 (0.1, 48.3
Body surface area involvement, %	10.0 (1.0, 33.0)	6.0 (1.0, 99.0)	5.0 (0.0, 90.0)
Disease stage			
IA	105 (35.2)	62 (20.8)	125 (41.9)
IB	75 (25.2)	39 (13.1)	78 (26.2)
IIA	6 (2.0)	5 (1.7)	9 (3.0)
IIB	15 (5.0)	13 (4.4)	19 (6.4)
III	5 (1.7)	4 (1.3)	5 (1.7)
IV	5 (1.7)	5 (1.7)	6 (2.0)
Unavailable	87 (29.2)	170 (57.0)	56 (18.8)
Prior therapies			
Skin-directed therapies		250 (83.9)	
Phototherapy		134 (45.0)	
Radiotherapy		44 (14.8)	
Topical chemotherapy		35 (11.7)	
Topical corticosteroids		177 (59.4)	
Topical retinoids		43 (14.4)	
Topical imiquimod		18 (6.0)	
Other topical treatment		46 (15.4)	
Systemic therapies		106 (35.6)	
Chemotherapy		27 (9.1)	
Retinoids		74 (24.8)	
HDAC inhibitors		22 (7.4)	
Extracorporeal photopheresis		10 (3.4)	
Other systemic treatment		36 (12.1)	

<table>
<tr><td></td><td>
<table>
<tr><td>Skin-directed and systemic therapies</td><td></td><td>95 (31.9)</td><td></td></tr>
<tr><td colspan="4">Concomitant therapy</td></tr>
<tr><td colspan="3">Skin-directed therapies</td><td>124 (41.6)</td></tr>
<tr><td colspan="3">Phototherapy</td><td>35 (11.7)</td></tr>
<tr><td colspan="3">Radiotherapy</td><td>12 (4.0)</td></tr>
<tr><td colspan="3">Topical chemotherapy</td><td>2 (0.7)</td></tr>
<tr><td colspan="3">Topical corticosteroids</td><td>70 (23.5)</td></tr>
<tr><td colspan="3">Topical retinoids</td><td>10 (3.4)</td></tr>
<tr><td colspan="3">Topical imiquimod</td><td>9 (3.0)</td></tr>
<tr><td colspan="3">Other topical</td><td>21 (7.0)</td></tr>
<tr><td colspan="3">Systemic therapies</td><td>48 (16.1)</td></tr>
<tr><td colspan="3">Chemotherapy</td><td>11 (3.7)</td></tr>
<tr><td colspan="3">Retinoids</td><td>30 (10.1)</td></tr>
<tr><td colspan="3">HDAC inhibitors</td><td>6 (2.0)</td></tr>
<tr><td colspan="3">Extracorporeal photopheresis</td><td>1 (0.3)</td></tr>
<tr><td colspan="3">Other</td><td>19 (6.4)</td></tr>
</table>
HDAC: histone deacetylase, NC: not collected.
*continuous data are presented as the median (range) and categorial data as number (%).
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary outcome (from clinicaltrials.gov (32)):
• Treatment responders using BSA at 12 months. Time Frame: 12 Months. The primary efficacy endpoint was the proportion of patients who are responders to treatment at the 12-month time point, using a ≥50% reduction from baseline in BSA as the definition of a responder in the group of patients who used mechlorethamine plus corticosteroids and possibly another treatment.
Other outcomes (from the abstract of the study by Kim et al. 2019):
• QoL. QoL was assessed with the SkinDex-29 questionnaire score at different time points (higher scores indicate greater negative impact).</td></tr>
<tr><td>Method of analysis</td><td>Clinical response was defined as proportion of responders (≥50% reduction from baseline in %BSA). QoL was assessed with the SkinDex-29 questionnaire at different time points. Number of AEs and the AEs affecting ≥3% of patients are also reported.</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

Table 26: Main characteristics of the study by El Sayed et al. 2019 (7)

Trial name	Efficacy of Doxycycline in the Treatment of Early Stages of Mycosis Fungoides: A Randomized Controlled Trial
NCT number	NCT03454945
Objective	Assessing the efficacy of doxycycline as a potential treatment modality for early stages of MF (33)
Publications – title, author, journal, year	Title: Efficacy of doxycycline in the treatment of early stages of mycosis fungoides: a randomized controlled trial Author: El Sayed et al. 2019

	Journal and year: Journal of Dermatological treatment 2019
Study type and design	Phase III, randomised, parallel assignment trial. Participants, care providers and investigators were masked in the trial.
Follow-up time	Patients were followed up at weeks four and eight, when mSWAT, CAILS and pruritus scoring were done. In addition, any possible side effects were assessed, reported, and managed accordingly. EOS was defined as achieving complete response or a maximum of three months (12 weeks) of treatment. After EOS there was an extended period where patients with progressive disease were shifted to PUVA, patients with partial response continued the same dose for another 12 weeks, while patients with stable disease received 400 mg daily for another 12 weeks. At the end of the extended treatment period, patients with the same or worsened response were shifted to PUVA.
Population (inclusion and exclusion criteria)	Inclusion criteria (from clinicaltrials.gov (33)): • Adults (above 18) of either sex with established diagnosis of classic MF Exclusion criteria (from clinicaltrials.gov (33)): • Any variant of MF other than the classic variant • Advanced stages of classic MF: Stage IIb, III or IV • Pregnant and lactating females • Patients with autoimmune diseases, e.g. systemic lupus erythematosus • Patients with solid or haematological malignancies, e.g. breast cancer, leukaemia etc. • Patients with any contraindications for doxycycline (such as liver disease, kidney disease, photosensitivity, peptic ulcer or patients receiving systemic retinoids) • Patients with any contraindication to phototherapy (such as any other skin cancers or photosensitivity); or to psoralen (such as liver disease) • No concomitant treatment was allowed except for Vaseline topical application (if needed).
Intervention	The intervention in the trial is doxycycline. The comparator is PUVA, which is the treatment arm we utilise in the assessment. Psoralen-UVA in 0.5 mg per kg 8-methoxypsoralen, starting dose: 1–3 J/cm^2 according to Fitzpatrick's skin type and increments of increase every other session of 0.5 J/cm^2 according to the degree of erythema and based on the guidelines of the Phototherapy Unit, Dermatology Department, Faculty of Medicine, Cairo University, Qasr El Eyni University Hospital. No concomitant treatment was allowed, except for Vaseline topical application (if needed).
Baseline characteristics	**Baseline characteristic*** / **Doxycycline (N=18)** / **PUVA (N=28)**

	Gender (M/F) – no. (%)	12 (66.7%) / 6 (33.3%)	5 (27.8%) / 13 (72.2%
	Age years – mean ± SD	38.94 ± 13.55	43.28 ± 10.18
	Duration of MF-CTCL (years) – Median (range)	5 (1-26)	9.50 (2-25)
	Disease stage – no. (%)		
	IA	3 (16.7%)	2 (11.1%)
	IB	13 (72.2%)	14 (77.8%)
	IIA	2 (11.1%)	2 (11.1%)
	mSWAT – Median (range)	36.5 (5-92)	46 (7-78)
	CAILS – mean ± SD	54.83 ± 16.35	56.5 ± 17.2
	Pruritus score – Median (range)	2.5 (0-8)	2 (0-5)
	DLQI score – Median (range)	6 (0-22)	7 (2-19)
	H&E score of MF – mean ± SD	5.97 ± 0.88	6.61 ± 1.4
	CD3 count/5HPF – Median (range)	713 (228-924)	356.5 (46-803)
	Bcl-2 count/5HPF – Median (range)	67 (0-273)	54 (2-217)
	*Data is presented as mean ± standard deviation if normally distributed and as range and median if non-normally distributed. H&E: Hematoxylin and Eosin, HPF: High Power Field.		

Primary and secondary endpoints

The primary endpoint (from clinicaltrials.gov (33)):

- Clinical assessment of the extent of the lesions in the body surface area (at three months). This was defined in terms of the ORR and was measured according to changes in mSWAT from baseline.

The secondary endpoints (from clinicaltrials.gov (33)):

- Pathological assessment using immunohistochemistry (at three months)
- From El Sayed et al. 2019: to compare the effect of doxycycline with PUVA in time to response (TTR - the time from the first dose till the patient first met a 50% decrease in mSWAT) and changes in CAILS, pruritus score, DLQI score, H&E score of MF, CD3 count and Bcl-2 count (7).

Method of analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. For quantitative data, data were described using mean and standard deviation if homogenous (normally distributed) and median and range if

	non-homogenous (non-normally distributed). Categorial data were presented using frequency (count) and relative frequency (percentage). Comparisons of quantitative variables between study groups were done using the Student t-test in homogenous data and the non-parametric Mann–Whitney test in non-homogenous data. For comparisons of serial measurements within each patient, paired t-test was used in homogenous data and the non-parametric Wilcoxon signed rank test was used in non-homogenous data. For comparing categorical data, Chi-square (x^2) test was performed. Exact test was used instead when the expected frequency was <5. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values <0.05 were considered as statistically significant. Since no patients were lost to follow-up, both primary treatment outcome (based on ITT analysis) and secondary treatment outcomes (based on per protocol analysis) used n=18 in their calculation.
Subgroup analyses	None

8.3 Overview of results per study

In the following, we present an overview of the results from included studies, which is used to assess the outcomes outlined in the DMC protocol.

Table 27: Results per study in Study 201

Trial name:	201 study									
NCT number:	NCT00168064									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Proportion with response (CR+PR) with mSWAT	Chlormethine 0.02% gel Chlormethine 0.02% ointment	130 130	46.9% (38.3%; 55.5%) 46.2% (37.6%; 54.7%)	0.7 %-point	-0.112; 0.127	Not reported.	RR: 1.017	0.783; 1.319	0.901	Absolute difference calculated by subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.
Proportion of patients who maintained response (CR+PR) with CAILS	Chlormethine 0.02% gel Chlormethine 0.02% ointment	76 62	85.5% (77.6%; 93.4%) 82.3% (72.7%; 91.8%)	3.2 %-points	-0.089; 0.162	Not reporter.	HR: 1.038			Absolute difference calculated by subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.
Adverse events – local	Chlormethine 0.02% gel	128	25.8% (18.2%; 33.4%)	9.3 %-points	-0.008;	Not reported.	1.559	0.956; 2.542	0.075	Absolute difference calculated by

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00
medicinraadet@medicinraadet.dk www.medicinraadet.dk

dermatitis irritation grade 3	Chlormethine 0.02% ointment	127	16.5% (10.1%; 23.0%)		0.191			subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.
Adverse events – Local dermatitis irritation grade 4	Chlormethine 0.02% gel Chlormethine 0.02% ointment	128 127	2.3% (-0.3%; 5.0%) 0.8% (-0.7%; 2.3%)	1.5 %-points	-0.023; 0.059	Not reported.	2.977	0.314; 28.234	0.342	Absolute difference calculated by subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.
Adverse events - SAEs	Chlormethine 0.02% gel Chlormethine 0.02% ointment	128 127	10.9% (5.5%; 16.3%) 8.7% (3.8%; 13.6%)	2.2 %-points	-0.053; 0.099	Not reported.	1.263	0.596; 2.675	0.542	Absolute difference calculated by subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.

Table 28: Results per study from the PROVe study

Trial name:	PROVe									
NCT number:	NCT02296164									
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**
				Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
QoL – Skindex-29 scores	Chlormethine gel	106	Emotions: 26.4	Emotions: -10.7		<0.001	NA	NA	NA	

between responder and non-responders at 12 months	(Valchlor) - responders		Symptoms: 26.8		Not reported.		
			Functioning: 13.2	Symptoms: -8.0	Not reported.	<0.001	
	Chlormethine gel (Valchlor) – non-responders	107	Emotions: 37.1				
			Symptoms: 34.8				
			Functioning: 22.8	Functioning: -9.6	Not reported.	<0.001	
QoL – Skindex-29 scores between responder and non-responders at 24 months	Chlormethine gel (Valchlor) responders	42	Emotions: 26.4	Emotions: -9.3	Not reported.	<0.001	NA NA NA
			Symptoms: 25.6				
			Functioning: 14.0	Symptoms: -10.0	Not reported.	<0.001	
	Chlormethine gel (Valchlor) non-responders	32	Emotions: 35.7				
			Symptoms: 35.6				
			Functioning: 22.6	Functioning: -8.6	Not reported.	<0.001	

Table 29: Results per study from the study by El Sayed et al. 2019 (7)

Trial name:	The study by El Sayed et al. 2019									
NCT number:	NCT03454945									
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**
				Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	

Proportion with CR+PR with mSWAT	PUVA	18	9 (50%, 95% Cl: 27%; 73%)	38.9%	0.087; 0.613	Not reported.	4.500	1.125; 17.993	0.033	Absolute difference calculated by subtracting the proportions in each study arm. Relative difference estimated as the risk ratio.
	Doxycycline	18	2 (11.1% 95% Cl: -3%; 26%)							

8.4 Results per PICO

Because the comparative analysis conducted in the current assessment is a narrative indirect comparison, we are not able to meaningfully fill out a results per PICO table.

Cost per patient and budget impact analysis of chlormethine (Ledaga®) for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients

Application to the Danish Medicines Council

25 February 2021

Company contact information

Fabian Schmidt
+ 33 787 41 66 09
SCHMIDT.F@recordati.com

Text marked with yellow is strictly confidential
and should be deleted before publication.

Table of content

List of abbreviations

AE	Adverse event
BAD	British Association of Dermatologists
BSA	Body surface area
CR	Complete response
CTCL	Cutaneous T-cell lymphoma
CU	Cost-utility
DMC	Danish Medicines Council
ECP	Extracorporeal photopheresis
FTU	Fingertip unit
HRQoL	Health-related-quality of life
IPD	Individual patient data
i.v.	Intravenous
MF	Mycosis fungoides
MF-CTCL	Mycosis fungoides-type T-cell lymphoma
mSWAT	Modified Severity Weighted Assessment Tool
NHS	National Health Service
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PPP	Pharmacy purchasing price
PR	Partial response
PROCLIPI	Prospective Cutaneous Lymphoma International Prognostic Index
PUVA	Psoralen and ultraviolet A
RCT	Randomised controlled trial
SD	Stable disease
SDT	Skin-directed treatment
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TNMB	Tumour-, node-, metastases and blood
UK	United Kingdom
UV	Ultraviolet
UV-B	Ultraviolet B

1 Background

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphomas (CTCL) and is a heterogenic group of rare non-Hodgkin-lymphomas (1). In the early stages of MF-CTCL, visible symptoms include patches and plaques. Patches are scaly and flat areas that can appear red or pink, while plaques are well-demarcated raised lesions that can be smooth or scaling and/or crusting (2–4). Both patches and plaques are highly itchy lesions, often localised in the lower abdomen, gluteal region and upper thighs (5). Patches can disappear, reappear or stay stable over time. In some individuals, patches progress to plaques (2,5). Plaques can turn into protruding tumours as MF-CTCL progresses (5). These tumours can ulcerate and bleed, which causes pain and discomfort for patients and increases the risk of infections (6,7). If more than 80% the body surface area (BSA) is affected, lesions are referred to as erythroderma (7).

Besides the physical burden, MF-CTCL patients also suffer under a substantial psychologic burden (8). Patients suffering from MF-CTCL have an increased risk of depression and anxiety compared to the general population, due to frustrations and worries about the severity and future course of their disease (8,9). MF-CTCL also affects the daily lives of patients suffering from the disease, their level of function and their productivity (8). The disease burden on patients increases as the disease progresses, with higher reductions in the health-related quality of life (HRQoL) in advanced stages of MF-CTCL (4).

MF-CTCL is classified according to the tumour-, node, metastases and blood (TNMB) system into stages from I-IV after the international Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer's criteria (10). An overview of the stages is provided in Table 1. The prognosis of MF-CTCL is stage-dependant. Early stages (IA and IB) have a good prognosis, and well-treated patients have a median survival of 35.5, 21.5 and 15.8 years in stage IA, IB and IIA, respectively. The median survival decreases as patients progress to more advanced stages. In stage IIB and III, the median survival is 4-6 years, and it is less than 4 years in stage IV. (1)

Current treatment of MF-CTCL follows international guidelines from the European Society for Medical and Oncology and the European Organisation for Research and Treatment of Cancer (11,12). No defined standard of care (SoC) exists, and treatment is individualised based on the cutaneous lymphoma's characteristics, the disease severity, patient performance status, comorbidities, earlier treatment etc. The treatment goals are to induce remission and postpone progression. A treatment course typically runs over several years.

Topical treatments like corticosteroids in combination with phototherapy (UV-B or psoralen and ultraviolet A (PUVA)) or nitrogen mustard is used in early stages (IA-IIA). However, these treatments have limitations. Phototherapy can only be offered for a limited number of treatments due to the UV radiation exposure, and prolonged treatment with corticosteroids can cause atrophy in the dermis or epidermis.

Table 1 **Overview and explanation of the different stages of MF-CTCL**

Stage	Explanation	Manifestations
IA	Less than 10% of the skin is involved.	The lymphoma is limited to the skin (patches or plaques).
IB	10% or more of the skin is involved.	
IIA	Patches or plaques are present on the skin and lymph nodes are enlarged, but they do not contain abnormal lymphoma cells.	
IIB	One or more protruding tumours in the skin. Lymph nodes can be enlarged, but they do not contain lymphoma cells.	
IIIA	Few or no lymphoma cells in the bloodstream (erythrodermic mycosis fungoides).	80% or more of the skin is involved with erythroderma (diffuse redness, thickening and possible fissuring of the skin), oedema, itching and sometimes pain. Lymph nodes can be enlarged but they do not contain lymphoma cells.
IIIB	A moderate number of lymphoma cells are present in the bloodstream.	
IVA	Numerous abnormal lymphoma cells are present in the blood stream (Sezary's syndrome) or the lymph nodes contain lymphoma cells. Lymphoma is present in the skin in the form of patches, plaques and/or erythroderma.	
IVB	The lymphoma has spread to other organs.	

Source: (1).

1.1 Chlormethine

Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells and induces apoptosis, primarily through DNA alkylation (13). Chlormethine induces DNA alkylation by binding to N7 guanine residues (potentially N3 adenine residues). The binding forms cross-links between guanine residues on opposite DNA strands (14,15). The unrepaired inter-strand cross-links included by chlormethine in the cell DNA prevent DNA transcription and replication, causing apoptosis (13,16,17). Chlormethine is also known as mechlorethamine and nitrogen mustard.

Chlormethine gel should be administered with a thin layer to affected areas once daily. According to the DMC protocol, the administration frequency of chlormethine can initially be lower and gradually increased to once daily. When a satisfactory response is achieved, the administration frequency can be reduced to once a week or once every other week.

Chlormethine treatment should be continued as long as the patient has a satisfactory response and tolerates treatment. If skin reactions emerge, treatment should be discontinued but can be initiated again at recovery. However, both the treatment duration and administration frequency are highly individualised among patients. (1) Additional information on the chlormethine gel can be found in Table 2.

Chlormethine (Ledaga) comes in tubes of 60 g 0.02% (160 µg/g) chlormethine gel and is used as a topical treatment of MF-CTCL. It can be used across disease stages and in combination with other treatments.

Table 2 **Chlormethine gel information**

Name	Ledaga
Active ingredient	Chlormethine
Indication	Topical treatment of adult patients with mycosis fungoides-type cutaneous T-cell lymphoma
Strengths and dosing	0.02% chlormethine gel for topical administration once daily
ATC-code	L01AA05
Packages	Tubes containing 60 g of chlormethine gel
EC date of approval	3 March 2017

Source: Summary of product characteristics (SmPC) on chlormethine gel (Ledaga) (13).

1.2 Patient population

MF-CTCL is a rare disease and more frequent in males than females. Patients are typically between 55-60 years of age when they develop MF-CTCL. In Denmark, approximately 400-500 patients have treatment-requiring CTCL and 60% have the MF type. In the Danish Medicines Council (DMC) protocol, the expert committee estimates that approximately 250-300 MF-CTCL patients (prevalence) would be candidates for chlormethine treatment and a yearly incidence of 30 new patients (1).

1.3 Clinical questions

The DMC protocol for assessing chlormethine gel for the treatment of MF-CTCL lists the following clinical questions:

1) *What is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B, and PUVA in adult patients with early stages (I-IIA) MF-CTCL, who have inadequate effect of at least one optimised topical treatment?*

2) *What is the value of chlormethine gel compared to topical corticosteroids, narrowband UV-B, and PUVA in adult patients with stage IIB-IV MF-CTCL or adult MF-CTCL patients (regardless of stage) with patches or plaques in the head/neck regions and the genitals, who have inadequate effect of at least one optimised topical treatment?*

2 Methods: Cost per patient analysis

The purpose of the cost per patient analysis was to estimate the incremental cost of treating MF-CTCL patients with chlormethine gel compared with phototherapy with narrowband UV-B or PUVA.

To estimate the cost per patient and answer the two clinical questions, we adapted a global cost-utility (CU) model of chlormethine gel to a Danish clinical setting. The global CU model was developed by the consultancy Costello Medical for Recordati Rare Diseases.

The adaption of the global CU model to a Danish clinical setting only involves the cost elements in the model. The model elements related to HRQoL measurements are not adjusted, as they are not applied in the cost per patient analysis. In the global model, three sheets have been added: "cost per patient", "budget impact" and "background", which contain the cost per patient analysis, the budget impact analysis, and a background sheet containing the information used for the different calculations, respectively. The sheets link to relevant cost information and results in the global CU model. The adjusted cells in the global model are marked with green to make it clear for the user which cells have been adjusted.

To inform the cost per patient analysis, a systematic literature search was conducted, and clinical experts were consulted. To inform the chlormethine gel arm, we identified Study 201, which is a phase II, randomised controlled trial investigating the efficacy (hereunder response to treatment) and safety of the chlormethine 0.02% gel compared with chlormethine 0.02% ointment in patients with MF-CTCL stage IA-IIA who had previously received treatment with at least one skin directed treatment (SDT). To inform the two phototherapy arms, efficacy estimates (response to treatment) on phototherapy were available from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) registry and a systematic literature review (SLR) and meta-analysis by Phan et al. 2019 (18). Recordati Rare Diseases was granted access to confidential data from the PROCLIPI registry for the United Kingdom (UK), and due to lack of Danish data, we assumed that data from UK MF-CTCL patients could be transferred to Danish MF-CTCL patients. As these data are confidential, all PROCLIPI inputs have been marked confidential (marked with yellow). The PROCLIPI registry is a prospective international registry for patients with CTCL, and the response rates available from the registry reflect real-world evidence of the effectiveness of phototherapy from UK clinical practice. The response definitions used were based on modified Severity Weighted Assessment Tool (mSWAT) score (an objective measure) and aligned to that used in Study 201.

The SLR and meta-analysis by Phan et al. 2019 aimed to compare the efficacy (and safety profile) of PUVA compared to narrowband UV-B in the treatment of early-stage MF-CTCL. There was some considerable limitations associated with Phan et al. 2019: the studies included were predominantly observational and retrospective in nature, and the majority of the studies in Phan et al. 2019 did not explicitly state that they used objective measures to determine response to

treatment (such as CAILS/mSWAT). (18) Therefore, it is likely that these studies evaluated response rates based on clinical experts making subjective decisions about whether patients have responded to treatment or not. This subjective judgement may lead to an overestimation of phototherapy efficacy. Moreover, the real-world PROCLIPI registry data indicate that the average estimates of responses derived from Phan et al. 2019 may represent an optimistic assessment of phototherapy efficacy. The proportion of patients achieving complete response (CR) and partial response (PR) on phototherapy in the studies included in Phan et al. 2019 seems to be particularly overestimated, relative to the estimates from the PROCLIPI registry. Based on this, efficacy estimates from the PROCLIPI registry was used in the base case to inform the PUVA and narrowband UV-B arms in terms of treatment response.

However, Phan et al. 2019 have the advantage of representing a SLR and meta-analysis that synthesises evidence from across several studies; therefore, a sensitivity analysis using Phan et al. 2019 to estimate phototherapy efficacy (treatment response) was be presented.

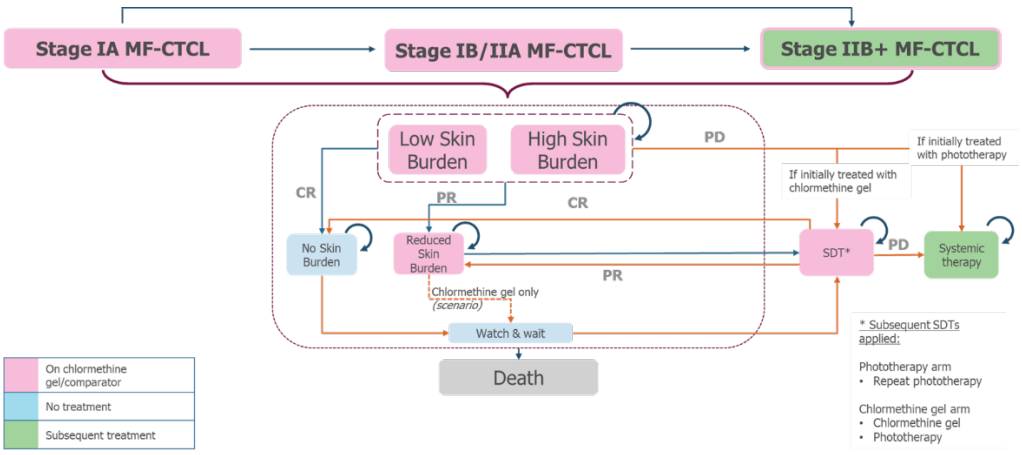
The model was also informed by the study by Agar et al. 2010 (19) and the summary of product characteristics (SmPC) on the included drugs. We also consulted the Danish clinical expert Professor Lars Iversen, who treats patients with MF-CTCL at Aarhus University Hospital.

In the DMC protocol on chlormethine gel, the expert committee requested a comparison of chlormethine gel and corticosteroids. Due to lack of adequate data on the effect of corticosteroids, it was not possible to conduct an analysis comparing chlormethine gel and corticosteroids. Thus, we will not present an incremental cost or budget impact analysis of treating MF-CTCL patients with chlormethine gel compared to corticosteroids. Moreover, we were not able to identify any data suitable for answering clinical question 2 in the DMC protocol on chlormethine gel. Therefore, the following sections and the results presented later in the current applications are all related to clinical question 1.

2.1 Applied model

The global CU model adapted for the cost per patient analysis is a cohort Markov model developed in Excel. An overview of the model structure is provided in Figure 1. The model consists of three disease stages and within each disease stage, patients move between various skin burden health states.

Figure 1 **Model structure, global cost-utility model**



Abbreviations: CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SDT: skin-directed therapy. Some arrows in the model are orange while others are blue. The colours of the arrows have no meaning.
Source: Global model, Costello Medical Consulting for Recordati Rare Diseases and Helsinn Healthcare, 2021.

Patients enter the model dependent on their MF-CTCL disease stage. They enter in either: stage IA, stage IB/IIA or stage IIB+ and can progress to a more advanced disease stage but can not regress. The baseline distribution of patients in the three disease stages were estimated based on data from the PROCLIPI registry and presented in Table 3.

In clinical question 1, only early stages of MF-CTCL were included and no patients entered the model in stage IIB+.

Table 3 **Distribution of MF-CTCL patients in the three disease stages at baseline**

Disease stage	Proportion
Stage IA	[redacted]
Stage IB/IIA	[redacted]
Stage IIB+	[redacted]

Source: The PROCLIPI registry.

Upon entering the model, patients were defined as having either low or high skin burden within each disease stage. The low/high distinction was based on the percentage of BSA affected: low skin burden was <10% BSA affected and high skin burden was 10-80% BSA affected (7). Patients with

>80% BSA affected were classed as erythrodermic and excluded from the model, because erythrodermic patients would not be considered for treatment with chlormethine gel. The BSA classifications are summarised in Table 4.

Table 4 **Classification of patients as having low or high skin burden in the model**

BSA affected	Classification
<10 %	Low skin burden
10-80%	High skin burden
>80%	Not included in the model

Source: (7).

Stage IA patients were assumed to have low skin burden at model entry, and stage IB/IIA patients were assumed to have high skin burden at model entry. Patients in stage IIB+ were assumed to consist of a combination of patients with low and high skin burden, based on data from the PROCLIPI registry. The distributions of patients between low/high skin burden categories in the disease stages are presented in Table 5.

Table 5 **Distribution of patients with <10% BSA and 10-80% BSA affected in the three disease stages.**

Skin burden	<10% BSA	10-80% BSA
Stage IA	100.00%	-
Stage IB/IIA	-	100.00%
Stage IIB+*	[redacted]	[redacted]

*Clinical question 1 only included patients with early stages of MF-CTCL and no patients would enter the model in stage IIB+.
Stage IA: As per the TNMB classification system, all stage IA patients have <10% BSA affected.
Stage IB/IIA: As per the TNMB classification system, all stage IB patients have >10% BSA affected. It is assumed that all stage IIA patients similarly have >10% BSA, based on the PROCLIPI registry.
Stage IIB+: PROCLIPI registry.
Source: Assumption.

2.1.1 Modelling of clinical efficacy in the CU model

Patients in the low and high skin burden health states within each disease stage were modelled to experience degrees of response to treatment, including remission, relapse of skin lesions or no change. Response to treatment was categorised as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), aligned to the response categories from Study 201 based on mSWAT. The response categories are presented in Table 6.

To avoid confusion, it should be noted that an outcome of PD on the mSWAT corresponds to a progression of skin symptoms (i.e. relapse of skin lesions) and should not be confused with progression of disease stage.

To avoid complexity of adapting the global model and since none of the included alternatives are subjected to a need of additional monitoring, we assumed that patients would be monitored and assessed for progression at the same time point for all included alternatives, which was sat to every four months.

Table 6 **Response categories for mSWAT in Study 201. Definitions are change from baseline.**

Response category	Definition
Complete response (CR)	mSWAT score of 0
Partial response (PR)	>50% reduction from baseline but not 0
Stable disease (SD)	< 50% reduction or < 25% increase from baseline
Progressive disease (PD)	≥25% increase from baseline

Source: Study 201 has been published in Lessin et al. 2013 (20).

2.1.2 Possible transitions in the model

In the following, we present the possible transitions in the model and how the transition probabilities were calculated. Transition probabilities are presented in section 2.1.3.

Transitions between the three MF-CTCL disease stages

Progression between the three MF-CTCL disease stages (IA, IB/IIA and IIB+) was treatment-independent, and transition probabilities were derived from Agar et al. 2010 in the base case, consistent with the source used to inform disease-specific mortality in the model (19). Although the use of this source requires the assumption that all stage IA patients are progressing to stage IB/IIA and all stage IB/IIA patients are progressing to stage IIB+ (as data on progression only provides data on what disease stage patients are progressing from but does not provide data on what disease stage patients are progressing to), this was considered to be an appropriate source given the relatively large sample size (n=1,502) and long duration of follow-up (median: 5.9 years). Estimated transition probabilities can be seen in Table 8.

Transitions between the health states

Patients in the three disease stages (IA, IB/IIA and IIB+) with low/high skin burden transitioned between the health states shown in Figure 1. In the absence of data, transition probabilities for patients in the advanced disease stages (IIB+) with low skin burden (<10% BSA) were assumed equal to those for stage IA (as all stage IA patients were assumed to have low skin burden). Transition probabilities for patients in the advanced disease stages with high skin burden (>10-

80%) were assumed equal to patients in stage IB/IIA (as all stage IB/IIA patients were assumed to have high skin burden). This assumption was considered reasonable because the model splits advanced disease stage patients into low or high skin burden to match either stage IA or stage IB/IIA, respectively, based on similar skin symptoms and therefore similar expected efficacy of included alternatives.

Time to response was required to derive the transition probabilities between health states. For chlormethine gel, mean time to response was calculated for each response type (CR, PR and CR following initial PR) based on patient-level data from Study 201. For PUVA, time to response was set to two months, based on the maximum treatment duration with PUVA of eight weeks according to identified Danish PUVA treatment guidelines (21,22). For narrowband UV-B time to response was set to three months, based on identified Danish treatment guidelines for narrowband UV-B (12 weeks) (23).

Transitions from low/high skin burden

Patients transitioned from the low/high skin burden health states to either "No skin burden", "Reduced skin burden" or "SDT", depending on the achieved treatment response (see Figure 1). For chlormethine gel, the transitions from the low/high health states to the above-mentioned health states were based on response rates from Study 201. For PUVA and narrowband UV-B, response rates (CR and PR) were derived from the PROCLIPI registry, and failed response (PD) was derived from Phan et al. 2019 (18).

Transition to "No skin burden": If patients with low/high skin burden achieved CR, they transitioned to "No skin burden" and discontinued treatment. The transition probabilities were calculated based on the number of patients who achieved a confirmed CR (excluding any patients who previously achieved a confirmed PR) and the time at which this first occurred from baseline (baseline was the first day the drug was dispensed). A confirmed response was the date of the evaluation at least 28 days after the first assessment of CR, i.e. second consecutive CR.

Transition to "Reduced skin burden": patients with low/high skin burden who achieved PR transitioned to this health state and remained on the same treatment. Transition probabilities were calculated based on the number of patients who achieved a confirmed PR, and time to this occurred from baseline (baseline was the first day the drug was dispensed). Confirmed response was the date of the evaluation at least 28 days after the first assessment of PR, i.e. second consecutive PR.

Transition to "SDT": patients with low/high skin burden could experience PD and transition to the "SDT" health state if they were initially treated with chlormethine gel. If they were initially treated with phototherapy and experienced PD, they would transition to "Systemic therapy". The transition probabilities were calculated based on the number of patients with PD by end of trial follow-up (12 months in Study 201). A patient was considered to have progressive disease (PD) if they never achieved a confirmed response (PR or CR) and their last recorded mSWAT score was ≥25% above baseline. The initial timepoint at which patients were assessed for treatment

discontinuation based on skin progression was six months, based on clinical expert's opinion that clinicians would treat for at least six months before discontinuing therapy due to lack of efficacy.

Transition from "No skin burden" to "Watch and wait" to "SDT" (relapse after CR): patients in the "No skin burden" could relapse and transition to the "Watch and wait" health state (and receive no treatment) and then to the "SDT" health state. Based on data for the duration of watch and wait periods from the PROCLIPI registry, patients who relapse after a CR enter the "Watch and wait" health state for eight months before entering the "SDT" health state. This reflects that once patients relapse after a CR they would likely not go back on treatment immediately. The study by Kim et al. 2003 was used for the transition of relapse post-CR for chlormethine gel (24). This was a trial investigating topical nitrogen mustard (chlormethine) in early stage MF-CTCL patients. Data were pooled across MF-CTCL disease stages. However, individual patient data (IPD) from Study 201 used in the calculation of relapse post PR indicate that no patients experienced PD following CR during the 12 months of follow-up of Study 201, suggesting that the use of Kim et al. 2003 may overestimate the rate of relapse following a CR with chlormethine gel. For phototherapy, relapse post CR was derived from Whittaker et al. 2012 (25), a randomised controlled trial (RCT) of PUVA alone versus PUVA plus bexarotene in stage IB/IIA MF-CTCL patients. Data from both treatment arms were used to maximise sample size as no significant difference was found between treatment arms for the proportion of patients relapsing post CR. Furthermore, data were pooled across disease stages.

Transitions from "Reduced skin burden" to "SDT" – relapse after PR: for estimating transitions for patients progressing following an initial PR, IPD from Study 201 were used. Specifically, this transition was informed by patients from Study 201 who had a single PD post PR. Data were pooled across disease stages due to the small sample size. Whilst the definition of PD in Study 201 outcomes excludes the assignment of PD to a patient who had previously achieved PR (i.e. PD was only defined if it occurred prior to CR or PR), using IPD from Study 201 has the advantage of alignment with the source used for the majority of the transitions for chlormethine gel in the model (as these come from Study 201). For phototherapy (both narrowband UV-B and PUVA), this transition was assumed to be the same as the transition for initial PD due to a lack of relevant data, i.e. this transition probability for phototherapy was assumed to be the same as the transition to "Systemic therapy" from the low and high skin burden health states.

Transition from "SDT" to "Systemic therapy": patients in the "SDT" health state could respond to treatment (CR, PR, and PD) or preserve stable disease and remain in the "SDT" health state. Transitions from the "SDT" health state when experiencing CR, PR or PD were assumed to be the same as when patients had first received treatment, because we were not able to identify data to inform the efficacy of repeated treatment (i.e. the efficacy of SDTs (chlormethine gel, phototherapy) when used as a second-line treatment). This means that the efficacy of the SDTs in the "SDT" health state was assumed to be the same as when those SDTs were modelled as first-line treatments. Therefore, these transitions were derived from mSWAT response rates from Study 201 for chlormethine gel, and response rates from the PROCLIPI registry for the two phototherapies.

Patients continued to transition between these subsequent health states throughout the model's time horizon. Over the time horizon, patients could progress through the three disease stages but not regress. Patients could transition to the "Death" health state from any other health state and from any of the three MF-CTCL disease stages. The likelihood of this transition was dependent on disease stage and independent of skin burden; the likelihood of entering the "Death" health state was equally likely from any skin burden health state.

2.1.3 Transition probabilities

Transition probabilities between the three MF-CTCL disease stages

Data on disease-specific survival at five years and risk of disease progression over five years from Agar et al. 2010 were used to calculate the assumed risk of disease progression among survivors at five years and the assumed risk of disease progression in years 0–5 (all presented in Table 7) (19). The assumed risk of disease progression in years 0–5 was then converted to a monthly transition probability and presented in Table 8.

Table 7 **Progression data from Agar et al. 2010**

	Disease-specific survival (%), 5 years	Risk of disease progression (%), 5 years	Assumed risk of disease progression among survivors, 5 years	Assumed risk of disease progression, years 0-5
Stage IA	98%	8%	6	0.06
Stage IB/IIA				
Stage IB	89%	21%	10	0.10
Stage IIA	89%	17%	6	0.06
Stage IIB+				
IIB	56%	48%	4	0.04
IIIA	54%	53%	7	0.07
IIIB	48%	82%	30	0.30
IVA1	41%	62%	3	0.03
IVA2	23%	77%	0	0.00
IVB	18%	82%	0	0.00

Source: Agar et al. 2010 (19).

Table 8 **Transition probabilities for the progressions between the three disease stages derived from Agar et al. 2010. The probabilities are treatment-independent and therefore the same for all treatment alternatives**

	End disease stage		
Start disease stage	**Stage IA**	**Stage IB/IIA**	**Stage IIB+**
Stage IA	0.9990	0.0010	0.0000
Stage IB/IIA	-	0.9984	0.0016
Stage IIB+	-	-	1.0000

Source: Calculations based on data from Agar et al. 2010 (19).

Alternative data for the transition probabilities between the three disease stages were derived from Wernham et al. 2015, a database study investigating disease progression in 86 patients with early MF-CTCL (26). This study is provided as an alternative, given the granularity of progression data available (i.e. including data on proportion of patients progressing, as well as what disease stage the patient progressed to). Specifically, data on the time to progression for stage IA and stage IB/IIA patients, in addition to data for the proportion of patients progressing to stage IB/IIA and to stage IIB+ from either stage IA or stage IB/IIA, were used to calculate the transition probabilities required, assuming an exponential distribution (i.e. constant with respect to time). Data from Wernham et al. 2015 are presented in Table 9 and the calculated transition probabilities are presented in Table 10. A sensitivity analysis with transition probabilities between disease stages measured with data from Wernham et al. 2015 will be presented.

Table 9 **Progression data from Wernham et al. 2015**

	Mean time to progression, months	Total number of patients	No progression	Progression to Stage IB/IIA	Progression to Stage IIB+
Stage IA	85	38	24	9	5
Stage IB/IIA	55	48	35	-	13

Source: Wernham et al. 2015 (26).

Table 10 **Transition probabilities between the three disease stages derived from Wernham et al. 2015**

	End disease stage		
Initial disease stage	**Stage IA**	**Stage IB/IIA**	**Stage IIB+**
Stage IA	0.9969	0.0028	0.0004
Stage IB/IIA	-	0.9951	0.0049
Stage IIB+	-	-	1.0000

Source: Wernham et al. 2015 (26).

Chlormethine gel: transition probabilities between the health states

In the following, we present the transition probabilities for chlormethine gel. The sources used and how the probabilities are derived have been described in section 2.1.2. Table 11, Table 12 and Table 13 show the probabilities of transitioning from one health state to another, for stage IA patients with low skin burden, stage IB/IIA patients with high skin burden and stage IIB+ patients with mixed low/high skin burden, respectively.

Table 11 **Chlormethine gel: between health states transition probabilities for patients with low skin burden in the IA disease stage**

	End health state					
Start health state	**Low skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
Low skin burden	0.919	0.008	0.066	-	0.007	-
No skin burden	-	0.969	-	0.031	-	-
Reduced skin burden	-	0.017	0.978	-	0.005	-
Watch & wait	-	-	-	0.882	0.118	-
SDT	-	0.041	0.103		0.845	0.010

Source: Study 201 (20), Kim et al 2003 (24) and PROCLIPI registry.

Table 12 **Chlormethine gel: between health states transition probabilities for patients with high skin burden in the IB/IIA disease stage**

	End health state					
Start health state	**High skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
High skin burden	0.838	0.000	0.153	-	0.010	-
No skin burden	-	0.969	-	0.031	-	-
Reduced skin burden	-	0.020	0.975	-	0.005	-
Watch & wait	-	-	-	0.882	0.118	-
SDT	-	0.035	0.173	-	0.768	0.024

Source: Study 201 (20), Kim et al 2003 (24) and PROCLIPI registry.

Table 13 **Chlormethine gel: between health states transition probabilities for patients with high and low skin burden in the IB/IIA disease stage**

	Low skin burden End health state					
Start health state	**Low skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
Low skin burden	0.919	0.008	0.066	-	0.007	-
No skin burden	-	0.969	-	0.031	-	-
Reduced skin burden	-	0.017	0.978	-	0.005	-
Watch & wait	-	-	-	0.882	0.118	-
SDT	-	0.041	0.103	-	0.845	0.010
	High skin burden End health state					
Start health state	**High skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
High skin burden	0.838	0.000	0.153	-	0.010	-
No skin burden	-	0.969	-	0.031	-	-
Reduced skin burden	-	0.020	0.975	-	0.005	-
Watch & wait	-	-	-	0.882	0.118	-
SDT	-	0.035	0.173	-	0.768	0.024

Source: Study 201 (20), Kim et al 2003 (24) and PROCLIPI registry.

Narrowband UV-B: transition probabilities between the health states

In the following, we present the transition probabilities for narrowband UV-B. The sources used and how the probabilities are derived have been described in section 2.1.2. Table 14, Table 15 and Table 16 show the probabilities for transitioning from one health state to another for stage IA patients with low skin burden, stage IB/IIA patients with high skin burden and stage IIB+ patients with mixed low/high skin burden, respectively.

Table 14 **Narrowband UV-B: between health states transition probabilities for patients with low skin burden in the IA disease stage**

	End health state					
Start health state	**Low skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
Low skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

Table 15 **Narrowband UV-B: between health states transition probabilities for patients with high skin burden in the IB/IIA disease stage**

	End health state					
Start health state	**High skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
High skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

Table 16 **Narrowband UV-B: between health states transition probabilities for patients with high and low skin burden in the IB/IIA disease stage**

	Low skin burden End health state					
Start health state						
Low skin burden						
No skin burden						
Reduced skin burden						
Watch & wait						
SDT						
Start health state						
High skin burden						
No skin burden						
Reduced skin burden						
Watch & wait						
SDT						

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

PUVA: transition probabilities between the health states

In the following, we present the transition probabilities between the health states for PUVA. The sources used and how the probabilities are derived have been described in section 2.1.2. Table 17, Table 18 and Table 19 show the probabilities for transitioning from one health state to another for stage IA patients with low skin burden, stage IB/IIA patients with high skin burden and stage IIB+ patients with mixed low/high skin burden, respectively.

Table 17 **PUVA: between health states transition probabilities for patients with low skin burden in the IA disease stage**

	End health state					
Start health state	**Low skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
Low skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

Table 18 **PUVA: between health states transition probabilities for patients with high skin burden in the IB/IIA disease stage**

	End health state					
Start health state	**High skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
High skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

Table 19 **PUVA: between health states transition probabilities for patients with high and low skin burden in the IB/IIA disease stage**

	End health state Low skin burden					
Start health state	**Low skin burden**	**No skin burden**	**Reduced skin burden**	**Watch & wait**	**SDT**	**Systemic therapy**
Low skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]			
Start health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced skin burden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Watch & wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: The PROCLIPI registry, Whittaker et al. 2012 (25), and Phan et al. 2019 (18).

2.1.4 Treatments applied to disease stages and health states

The different colours of the three disease stages and health states in Figure 1 represent the treatments that patients are assumed to receive in the different disease stages and heath states. In the pink stages/states, patients only receive chlormethine gel or one of the outlined comparators, while in the blue stages/states, they do not receive any treatment. The IIB+ disease stage (representing advanced stages) is both green and pink, as patients were assumed to receive active treatment for the underlying cancer, i.e. systemic therapies (bexarotene, extracorporeal photopheresis (ECP), gemcitabine, methotrexate or pegylated interferon (IFN-α) in addition to their treatment for skin lesions. This was done to reflect the background context in which chlormethine gel and relevant comparators would be used in advanced disease stages (treating skin symptoms and not the underlying cancer).

The background treatments in advanced disease stages varied based on the treatment a patient was receiving and the health state in which they reside. The green colour of the "Systemic therapy" health state indicates that patients have moved on to receive subsequent therapy with systemic therapies when transitioning to this health state. Differences in treatment effects

between chlormethine gel and the comparators of the subsequent systemic therapies is modelled to impact skin symptoms only, i.e. no difference in treatment effects between chlormethine gel and comparators is applied with regards to treatment of the underlying disease. This reflects the fact that in the advanced disease stages, chlormethine gel would be used for its impact on skin symptoms rather than underlying disease and would therefore be used in combination with subsequent systemic therapies.

Subsequent therapies

Subsequent therapies were applied in the "SDT" and "Systemic therapy" health states. In the "SDT" health state, the subsequent therapies were still SDT and depended on which treatments patients had received as first-line SDT treatment and on the health state to and from which a patient transitioned. Patients treated with chlormethine gel who transitioned from the low/high skin burden health state or "Watch and wait" health state to the "SDT" health state were modelled to receive treatment with either chlormethine gel or phototherapy. According to clinical expert's opinion, all patients who progress on first-line treatment with chlormethine gel would receive phototherapy as second-line SDT. Therefore, based on data from Study 201 suggesting that ~20% of patients progress on treatment with chlormethine gel and move on to receive phototherapy, it was assumed that in the "SDT" health state, 20% of patients previously treated with chlormethine gel would receive phototherapy and 80% (entering from the "Watch and wait or "Reduced skin burden" health states) would receive chlormethine gel. Upon entering the "SDT" health state, patients in the phototherapy arms could receive subsequent treatment with repeated phototherapy, as patients on phototherapy can only enter the "SDT" health state from the "Reduced skin burden" or "Watch and wait" health states.

Patients who progressed (PD) on initial phototherapy were modelled to transition from low/high skin burden to the "Systemic therapy" health state. This was based on clinical expert opinion, stating that patients who do not respond to phototherapy at all would not receive repeated phototherapy but would instead move to systemic therapies. Patients who progressed from the "SDT" health state regardless of previously received treatment also transitioned to the "Systemic therapy" health state. In this state, patients were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split.

Background treatment in advanced MF-CTCL disease stages

As seen in Figure 1, patients in the advanced disease stages (stage IIB+) would not be treated solely with SDTs, as they would also receive systemic therapies for treating the underlying disease (shown by the mix of pink and green stage colour). The specific combinations of therapies that would be used in advanced disease stages are many and highly specific to the individual patient (considering patient preferences, treatment history and specific disease context). Therefore, it was not feasible to model specific combinations of SDTs and systemic therapies for advanced disease stages within the context of this model (a model that is focused on assessing treatment benefit on the skin symptoms of MF-CTCL and not the underlying disease). Based on this, patients in advanced disease stages were assumed to receive systemic treatment

for their underlying disease in addition to their skin lesion treatments, and this systemic background treatment was modelled as a bundle of treatments including bexarotene, ECP, gemcitabine, methotrexate and brentuximab vedotin, weighted according to data from the PROCLIPI registry on the most common treatments prescribed among advanced stage MF-CTCL patients in UK clinical practice. The Danish clinical expert verified that these treatments are also used for treating the underlying disease in advanced stages in a Danish setting. The advanced disease treatment bundle was varied based on the treatment a patient was receiving and the health state in which they resided:

- Chlormethine gel: two types of treatment bundles were modelled for patients with advanced disease and on chlormethine gel. One treatment bundle was applied to patients with advanced disease residing in the "Systemic therapy" health state. This advanced disease treatment bundle did not include pegylated IFN-α and bexarotene to avoid double-counting, because bexarotene and pegylated IFN- α were already applied to the "Systemic therapy" health state. The other bundle contained bexarotene, ECP, gemcitabine, methotrexate, pegylated IFN-α and brentuximab vedotin, and was applied to all other health states in the advanced disease stages.
- PUVA and narrowband UV-B: three types of advanced disease stage background treatment bundles were modelled. One bundle was applied to patients in the "Systemic therapy" health state (this treatment bundle did not include pegylated IFN-α or bexarotene to avoid double-counting as for chlormethine gel). The other two bundles covered the other health states and depended on whether the patient was actively receiving phototherapy or not. If the patient was not receiving phototherapy (e.g. resided in the "No skin burden" health state, or after maximum treatment duration with PUVA), they received a treatment bundle containing bexarotene, ECP, gemcitabine, methotrexate, pegylated IFN-α or brentuximab vedotin. If the patient was on phototherapy, they received the bundle without methotrexate and ECP to reflect the contraindication to these therapies for patients receiving phototherapy.

Due to lack of data, we assumed that the proportions of patients receiving these bundles of treatments in the model are the same for the two phototherapies (PUVA and narrowband UV-B) and the same for chlormethine gel. The proportions ascribed to each treatment in the bundle are presented for chlormethine gel and comparators in Table 20 and Table 21, respectively. It was assumed that patients receive these treatments until they transition to the "Death" health state.

Table 20 **Chlormethine gel: proportions of patients receiving the background treatments in the advanced disease stages in the model**

Treatment	Proportion on the different background treatments while on chlormethine gel (initial treatment)	Proportion on the different background treatments in subsequent health states*
Brentuximab vedotin	[redacted]	[redacted]
Pegylated IFN-α	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Oral Bexarotene	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]

Source: The PROCLIPI registry.
*Patients who progress from first-line treatment move to "Systemic therapy" and receive bexarotene and pegylated IFN-α. Therefore, they will not receive these treatments in the subsequent health states in advanced disease stages.

Table 21 **Narrowband UV-B and PUVA: proportions of patients receiving the background treatments in the model**

Treatment	Advanced disease (% while on PUVA and UV-B)	Advanced disease (% post-PUVA or UV-B)	Advanced disease (% in Systemic therapy)
Brentuximab vedotin	[redacted]	[redacted]	[redacted]
Pegylated IFN-α	[redacted]	[redacted]	[redacted]
ECP*	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Oral Bexarotene	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]

Source: The PROCLIPI registry.
*Patients could not receive treatment with ECP and methotrexate at the same time as they received phototherapy.

2.1.5 Modelling of mortality

Disease presentation and patient prognosis differ by disease stage and severity of skin lesions. Patients with early stage disease may have a very good prognosis, with five-year progression free survival (PFS) rates ranging from 75–95% and overall survival (OS) from 78–97%. The likelihood of progression increases with disease stage, and prognosis is poor in advanced stages of disease (27).

OS data for the three disease stages was derived from median survival by disease stage data from Agar et al. 2010 (19). Estimates of the number of patients at each disease stage in UK clinical practice from the PROCLIPI registry were used to derive weighted median survival in months for

patients in each disease stage (i.e. weighted averages for IB/IIA and IIB+). This was subsequently used to derive transition probabilities for use in the model, assuming an exponential distribution. In addition to transition probabilities to the "Death" health state, to account for disease-specific mortality, baseline general population mortality from the Danish general population (by single year of age and by gender) was applied. A built-in constraint was applied to ensure that the modelled (i.e. disease-specific) mortality did not drop below that of the general population mortality at any time point. The median survival data from Agar et al. 2010 and the number of patients in each disease stage from the PROCLIPI registry are presented in Table 22.

Table 22 **Median survival by disease stage in the model**

Clinical stage	N	Median survival (years)	Weighted median survival (years)	Weighted median survival (months)
Stage IB/IIA				
IB	[redacted]	21.50		
IIA	[redacted]	15.80	[redacted]	[redacted]
Stage IIB-IV				
IIB	[redacted]	4.70		
IIIA	[redacted]	4.70		
IIIB	[redacted]	3.40	[redacted]	[redacted]
IVA1	[redacted]	3-80		
IVA2	[redacted]	2.10		
IVB	[redacted]	1.40		

Source: Agar et al. 2010 (19) and the PROCLIPI registry.

Table 23 **Transition probabilities to the Death state in the model.**

Transitions	Transition probabilities
Stage IA to Death	0.0016
Stage IB/IIA to Death	0.0028
Stage IIB+ to Death	0.0147

Source: Agar et al. 2010 (19) and PROCLIPI registry.

2.1.6 Adverse events in the model

Adverse events (AEs) of grade 3 or higher that occurred in at least 5% of patients for chlormethine gel or the comparators were included in the model, as it was assumed that these AEs would be associated with a substantial healthcare sector cost.

Information on AEs for chlormethine gel was derived from the safety set from Study 201 and from Whittaker et al. 2012 for the phototherapies (20,25). Due to the available data, it was not possible to conduct a robust indirect comparison; therefore, a naïve comparison of frequencies of AEs reported in the respective sources was applied. Due to lack of data, the same AE frequencies for PUVA from Whittaker et al. 2012 were applied to narrowband UV-B.

Whittaker et al. 2012 (25) did not report any AEs of Grade 3 or Grade 4 severity occurring in ≥5% of patients treated with PUVA monotherapy, and therefore no AEs were assumed for PUVA in the model. Although phototherapy is not directly associated with significant AEs with short-term use, the use of phototherapy is not without a risk of AEs or serious AEs. An increased risk of secondary malignancies (i.e. melanoma) has been associated with the use of phototherapy where exposure is too high, or the number of repeated courses is too great.

We consulted the Danish clinical expert, who asserted that patients should not receive more than 200 PUVA treatments per lifetime due to the risk of skin cancers. A limit of 200 PUVA treatments per lifetime was not incorporated in the model because this had an insignificant impact on the result of the cost per patient analysis. The rationale was that in only a few cases, the maximum of PUVA treatments received over a lifetime would exceed 200. Due to discounting, the impact on the result was very small (as the treatments surpassing 200 would be far out in the future). Thus, it was not incorporated in the model. In Danish clinical practice, the use of PUVA is limited to treatment courses of eight weeks (21,22). In the model, a maximum of eight weeks of treatment with PUVA is included in alignment with this; acknowledging that this restriction to treatment duration recommendation seeks to mitigate the risk of secondary malignancies with phototherapy, the model assumes no occurrence of secondary malignancies with phototherapy. However, it must be noted that the estimates of PUVA efficacy in the model is not based on the Danish clinical practise for PUVA treatment, but came from the PROCLIPI registry, where PUVA courses were longer. This might overestimate the efficacy of PUVA and is a limitation in our analysis.

The consultation of the Danish clinical expert did not lead to inclusion of other AEs associated with any of the comparators. The frequency of AEs in the model is presented in Table 24 and was converted to the monthly probabilities presented in Table 25.

Table 24 **Frequency of AEs in the model**

AE	Chlormethine gel (%)	Narrowband UV-B (%)	PUVA (%)
Dermatitis (contact)	[redacted]	0%	0%
Erythema	[redacted]	0%	0%
Skin irritation	[redacted]	0%	0%

Source: Study 201 clinical study report for chlormethine gel and Whittaker et al. 2012 for PUVA and narrowband UV-B.

Table 25 **Monthly probabilities for AEs**

Adverse event	Chlormethine gel	PUVA	Narrowband UV-B
Dermatitis contact	0.47%	0%	0%
Erythema	0.47%	0%	0%
Skin irritation	1.03%	0%	0%

Source: Calculated based on data fron Study 201 (20).

2.2 Intervention

The intervention is topical chlormethine 0.02% gel. According to the SmPC, chlormethine gel should be administered to affected lesions in a thin layer once daily (13). As no specific dose is defined, the actual amount of applied gel per daily application is highly individual and uncertain. In the base case, we applied a daily dose of 2.21 g, which was the mean daily usage of chlormethine gel in Study 201, according to patient-level data analysis based on the 201 study dataset (20). This also means that in the base case, we assume no difference in daily dose between patients with low or high skin burden, i.e. no difference in chlormethine gel usage between disease stages. We present a sensitivity analysis where we assume a difference in daily dose between low/high skin burden.

2.3 Comparator

The comparators in the cost per patient analysis in both clinical question 1 and clinical question 2 are phototherapy with narrowband UV-B and PUVA.

PUVA

PUVA comprises oral psoralen (sold as tablets under the name Meladinine) followed by phototherapy with UV-A. In a Danish clinical setting, patients receive PUVA three to two times per week with varying treatment durations. The availability of PUVA in Denmark is limited, and therefore, information on the treatment course is limited. At the Region hospital in Viborg, PUVA guidelines state that patients should receive PUVA two times per week for approximately 1.5 to 2 months (22). At the dermatology department of Zealand University Hospital in Roskilde, PUVA guidelines state that treatment should be given two to three times per week for four to ten weeks (21). Based on this, we assumeed that patients in a Danish clinical setting on average receive PUVA two times per week for eight weeks per treatment course. A sensitivity analysis with other treatment frequencies and treatment durations will be conducted.

Narrowband UV-B

According to the Danish clinical expert, patients usually start treatment with narrowband UV-B three times per week for ten weeks (25-30 treatments per treatment course). After the ten weeks, the treatment frequency can be reduced to one treatment per week for approximately 15 to 20 weeks. Most patients have 40-50 treatments in total in a full treatment course.

Corticosteroids

As mentioned, we were not able to include corticosteroids in the analysis due to lack of adequate data on the effect of corticosteroids in MF-CTCL patients.

2.4 Patient population in the model

The baseline characteristics of the modelled cohort are based on patient data from Study 201 and the PROCLIPI registry and presented in Table 26.

It is not clearly specified in the PROCLIPI registry if patients have had inadequate effect of at least one previously optimised topical treatment, which is the desired patient population in the protocol on chlormethine gel. However, many patients with MF-CTCL initially receive topical steroids since, before being diagnosed, the pathology of MF-CTCL manifests in skin symptoms that physicians and more particularly dermatologists are used to treat with topical corticosteroids. Once the diagnosis is made, corticosteroids (class 1 to 4) always play a role in the management of skin lesions given their anti-inflammatory properties and may well be used concomitantly with other SDTs. Therefore, we find it acceptable to assume that patients in the PROCLIPI registry have previously received treatment with corticosteroids. Thus, we regard the PROCLIPI registry as the best available evidence for informing the phototherapy arms in the model and find it acceptable for answering clinical question 1. Moreover, it is not known if the effect of any of the treatment alternatives included in the model would be different in patients who previously had inadequate effect of at least one optimised topical treatment.

Table 26 **Patient characteristics in the global CU model**

Model parameter	Value		Source
Age, mean (SD)	[redacted]		Study 201 clinical study report (CSR); pooled data across treatment arms
Proportion who are female	[redacted]		
Mean BSA, m^2	1.91*		NHS Health Survey for England 2017: Adult Health, approximated from height and weight using Du Bois formula (28). Assumed to be transferable to Danish patients.
Mean weight, kg	79.96*		NHS Health Survey for England 2017: Adult Health(28). Assumed to be transferable to Danish patients.
Disease stage			
Stage IA	[redacted]		PROCLIPI registry
Stage IB/IIA	[redacted]		PROCLIPI registry
Stage IIB–IV	[redacted]		PROCLIPI registry
Skin burden	<10% BSA	10–80% BSA	
Stage IA	100%	-	As per the TNMB classification system, all stage IA patients have <10% BSA affected (7).
Stage IB/IIA	-	100%**	As per the TNMB classification system, all Stage IB patients have >10% BSA affected. Based on PROCLIPI, [redacted] Stage IIA patients similarly have >10% BSA (7).
Stage IIB–IV	[redacted]	[redacted]	PROCLIPI registry

*The source of the mean BSA and mean weight was the National Health Service (NHS) Health Survey for England 2017: Adult Health, approximated from height and weight using Du Bois formula. We assumed these numbers to be transferable to Danish patients.
**As previously described, while stage IIA–IV patients can have either <10% or at least 10% BSA affected, based on data from PROCLIPI, [redacted] stage IIA patients [redacted] have at least 10% BSA affected, and therefore stage IB/IIA patients were all assumed to have high skin burden at model entry, given that this reflects the skin burden of all stage IB patients (who have high skin burden by definition) and a majority of stage IIA patients.

2.5 Applied perspective

A limited societal perspective was applied in the cost per patient analysis, in accordance with DMC guidelines (29).

2.6 Time horizon and cycle length

The CU model applies a lifetime time horizon in the base case. The rationale for the lifelong time horizon was that MF-CTCL is characterised by slow disease progression, meaning a lifetime time

horizon will allow all relevant differences between treatment arms to be captured, in accordance with DMC guidelines. Shorter time horizons (20 years) were explored in a sensitivity analysis. A monthly cycle length was applied in the base case to align with the assessment timepoints utilised in Study 201. Half-cycle correction was applied.

2.7 Discounting

Costs incurred after year 1 to year 35 are discounted by 3.5% per year and costs incurred from year 36 and thereafter discounted with 2.5% per year, in accordance with the Danish Ministry of Finance's guidelines for economic analyses (30).

2.8 Resource use and unit costs

The cost per patient analysis of chlormethine gel includes drug costs, hospital costs (including monitoring costs), AE costs, end-of-life costs and patient and transportation costs. Cross-sectional costs (i.e. cost incurred in the primary healthcare sector and municipalities) are not included in the analysis, because a cross-sectional resource use associated with any of the included alternatives was not identified.

2.8.1 Drug costs

The included drug costs were the costs of chlormethine gel, systemic subsequent treatments, and background treatments in advanced MF-CTCL disease stages (IIB+). The drug costs were based on the pharmacy purchasing prices (PPP) and obtained from www.medicinpriser.dk (February 2021). In the following, we describe how we estimated the costs of included drugs in the cost per patient analysis. An overview of included drugs is provided in Table 27.

Table 27 **Drug information**

Treatment	Strength (mg)	Package size	PPP (DKK)
Chlormethine gel	160 µg	Tubes of 60 g gel	17,800.00
Bexarotene (Targretin)	75 mg	100 capsules	8,084.04
Pegylated IFN-α-2a (Pegasys)	180 µg	4 vials	4,996.28
Methotrexate	2.5 mg	100 tablets	79.50
Brentuximab vedotin (Adcetris)	50 mg	1 vial	21,088.65
Gemcitabine	10 mg per mg	220 ml infusion bag	420.00

Source: www.pro.medicin.dk and www.medicinpriser.dk (February 2021).

Drug costs of chlormethine gel

As mentioned in section 2.2, we applied a daily dose of 2.21 g chlormethine 0.02% gel to all patients in the model in the base case. Chlormethine 0.02% gel is available in tubes of 60 g gel, and we estimated a yearly consumption of 13.45 tubes in the base case. The duration of treatment depended on response to treatment, i.e. the health state in which a patient resided.

Drug costs of included comparators

The costs of PUVA and narrowband UV-B are described under "Hospital costs".

Drug costs of systemic subsequent treatments

When patients experience PD and transition to the "Systemic therapy" health state, it was assumed that patients would receive either bexarotene or pegylated IFN-α in a 50:50 split, which was verified by the Danish clinical expert. The dose of bexarotene depends on BSA, with adult patients receiving 300 mg/m^2 once daily. According to the SmPC on bexarotene, the total daily dose of patients with a BSA between 1.88-2.12 m^2 is 600 mg (eight bexarotene 75 mg capsules) (31).

The dose of pegylated IFN-α used in MF-CTCL patients is 1.5 µg per kg subcutaneously once weekly, according to the study by Spaccarelli et al. 2015 (32). The average BSA and weight of the patient population in the model can be seen in Table 26. The applied PPPs of the two drugs are presented in Table 27.

Table 28 **Systemic subsequent therapies applied to the "Systemic therapy" health state**

Treatment	Dose per administration	Administrations per cycle	Cost (DKK) per cycle
Bexarotene (Targretin)	600 mg	30.44	19,685
Peg. IFN-α-2a (Pegasys)	119.94 µg	4.35	5,431

Source: Bexarotene: SmPC (31), peg. IFN-α: Spaccarelli et al. 2015 (32) and calculations with average BSA and average weight of the patient cohort.

Drug costs of background treatments for advanced MF-CTCL stages (IIB+)

As mentioned, patients with advanced MF-CTCL (stage IIB+) would not be treated with SDTs alone (such as chlormethine gel and the phototherapies) but would also receive treatment for their underlying disease. In the model, background treatment of underlying disease includes: brentuximab vedotin, pegylated IFN-α, ECP, methotrexate, bexarotene and gemcitabine. Information on pegylated IFN-α and bexarotene is presented above, and information on ECP can be found under "Hospital costs". According to www.pro.medicin.dk, the dose of gemcitabine is 1,000-1,250 mg per m^2 intravenously over 30 minutes once weekly for seven weeks, followed by a one-week break (33). The average BSA of the patient population in the model was 1.91 m^2, and we calculated a dose per administration of 2,149 mg (rounded number). The dose of brentuximab vedotin is 1.8 mg per kg intravenously over 30 minutes every three weeks (34). The average

weight of the patient population in the model was 79.96 kg, and we calculated a dose per administration of 144 mg (rounded number). We applied an oral dose of 23.44 mg methotrexate administrated once a week.

Table 29 **Background treatments applied to patients in the advanced disease stages (IIB+) in the model**

Treatments	Dose per administration	Administrations per cycle	Cost per cycle (DKK)
Methotrexate	23.44 mg	4.35	32
Gemcitabine	2,149 mg	3.26	1,370
Brentuximab vedotin	144 mg	1.45	91,698

Source: British National Formulary for methotrexate, www.pro.medicin.dk and brentuximab vedotin SmPC.
Please note that numbers are rounded for Gemcitabine and Brentuximab vedotin.

2.8.2 Hospital costs

PUVA and narrowband UV-B treatment

Hospital costs associated with treating MF-CTCL patients with PUVA and narrowband UV-B were included in the cost per patient analysis. Furthermore, hospital costs associated with the background treatments in the advanced disease stages were also included.

Patients receiving PUVA and narrowband UV-B treatment are treated at the hospital. To estimate the hospital cost associated with PUVA treatment, we applied a PUVA treatment regimen of two times per week for eight weeks (1.84 cycles), based on PUVA guidelines from the University hospital of Zealand in Roskilde and Hospitalsenhed Midt (21,22). To estimate the cost of narrowband UV-B, we applied an UV-B treatment guideline from the University hospital of Zealand in Roskilde and statements from the Danish clinical expert. Narrowband UV-B treatment three times per week for ten weeks was applied in the base case (2.76 cycles).

The unit cost of PUVA and narrowband UV-B treatments was based on the DRG tariff 2021 "17MA98" of 3,203 DKK per treatment. The unit cost applied in the base case, and the estimated hospital costs per cycle associated with PUVA and narrowband UV-B treatment are presented in Table 30 and Table 31, respectively.

Table 30 **Identified cost per phototherapy treatment**

	PUVA	Narrowband UV-B
DRG tariff 2021 17MA98 (DKK)	3,203	3,203

Table 31 **Hospital costs associated with PUVA and narrowband UV-B treatment**

Treatment	Treatments per cycle	Treatment costs per cycle (DKK)
PUVA	8.7	31,047
Narrowband UV-B	13.04	46,570

Source: University hospital of Zealand (21), Hospitalsenhed midt (22), DRG tariff 2021 (17MA98).

Background treatments

ECP, gemcitabine and brentuximab vedotin, included as background treatments in the advanced disease stages, require treatment at the hospital. No hospital costs associated with pegylated IFN-α treatment is applied, because we assume that patients self-inject the medication.

We identified the DRG tariff 2021 "17MA98" of 3,203 DKK, which we applied as the treatment cost for ECP. To estimate the hospital cost associated with treating patients with gemcitabine and brentuximab vedotin, we applied the DRG tariff 2021 "17MA98" of 3,203 DKK. Treatment frequencies per cycle for gemcitabine was sourced by www.pro.medicin.dk (February 2021). No guidelines on the frequency of ECP treatment in a Danish setting could be identified; therefore we applied information from the British Association of Dermatologists (BAD) guideline (7). Information on treatment frequencies for brentuximab vedotin came from the SmPC (34).

Table 32 **Hospital costs associated with brentuximab vedotin and gemcitabine treatment**

	DRG tariff (DKK)	Treatment frequency per cycle	Cost per cycle (DKK)
Brentuximab vedotin	3,203	1.45	5,174
Gemcitabine	3,203	3.26	11,643
ECP	3,203	2.17	7,762

DRG tariff applied for ECP, gemcitabine and brentuximab vedotin administrations: 17MA98.
Source: interaktivdrg.sundhedsdata.dk, BAD guidelines, www-pro-medicine.dk and the SmPC on brentuximab vedotin.

Monitoring and assessing treatment progression

We included costs for monitoring patients (control visits) and assessment for disease progression. These costs were also applied in the cycles where patients did not receive treatment with the included alternatives. The timepoint for monitoring and assessing progression were assumed to be every three months for all included alternatives. We applied the DRG tariff "17MA98" of 3,203 DKK to estimate a hospital cost for monitoring patients and assessing progression. These costs are calculated in the "Background" sheet in the Excel model. It should be noted that the sheet "Monitoring & Resource use" in the global model are not utilised for estimating monitoring costs because the resource use listed in this sheet is from a UK clinical setting. Furthermore, these

inputs are disease stage specific (i.e. depends on if a patient is in disease stage IA, IB/IIA or IIB+) and are not treatment depended.

2.8.3 Adverse events costs

The AEs included in the model were presented in Table 24 and Table 25. Due to the nature and treatment of the AEs included in the model, we included one outpatient visit when patients experienced an AE and assumed that the AEs would be managed during this visit. AEs were only included in the chlormethine gel arm. The unit costs used to estimate an AE cost are presented in Table 33.

Table 33 **AE costs in the cost per patient analysis**

	DRG tariff	Cost per cycle in chlormethine gel arm
Dermatitis (contact)	17MA98	3,203
Erythema	17MA98	3,203
Skin irritation	17MA98	3,203

Source: DRG tariff 2021, Assumption.

2.8.4 End-of-life costs

Patients who transition to the "Death" health state incur a one-time end-of-life cost. This cost represents the cost of palliative care of MF-CTCL patients at the hospital. The end-of-life cost is set to the DRG-tariff "17MA01" of 43,901 DKK.

2.8.5 Patient and transportation costs

Patient and transportation costs were included in accordance with DMC guidelines (29). A unit cost of 179 DKK per hour was used in the estimation of the cost of patient time and a unit cost of 3.52 DKK per km was used in the estimation of transportation costs (35). Based on DMC guidelines, an average driving distance of 14 km each way to the hospital was assumed, summarising to a total of 28 km. 30 minutes of patient time each way to the hospital was assumed, summarising to a total of one hour of patient time spent on transportation to the hospital (29). Patient and transportation costs were associated with patients traveling to outpatient/treatment visits at the hospital and receiving treatments.

No patient or transportation time was assumed to be associated with treatment with chlormethine gel due to the topical administration. The treatment time of phototherapy with UV-A and narrowband UV-B is very short (patients start with a few seconds and increases to five to seven minutes (22)). Based on this, we assume an average of 30 minutes of patient time associated with receiving PUVA and narrowband UV-B treatment, including treatment time,

undressing time and waiting time. The total patient time associated with treatment with phototherapy (both PUVA and narrowband UV-B) was therefore assumed to be 1.5 hours. Patient and transportation costs were also included for the hospital visits for monitoring and assessing patients for progression.

It should be noted that PUVA is only available at a limited number of facilities in Denmark and some patients must travel a long way to receive PUVA treatment. We will not present a sensitivity analysis increasing the patient and transportation time associated with PUVA treatment, because these costs have a very limited impact on the total cost of PUVA treatment and estimates would be highly uncertain.

As mentioned, patients receive the background treatments (brentuximab vedotin, gemcitabine and ECP) at the hospital. We have applied patient and transportation costs to these treatments. Both brentuximab vedotin and gemcitabine are infused intravenously for 30 minutes. We were not able to identify any references on the treatment duration for ECP and therefore, we assumed the same treatment duration for ECP as for gemcitabine and brentuximab vedotin and a total of 1.5 hours of patient time was applied to all three background treatments which comprised of patient time to transportation and receiving treatment (see Table 34).

Table 34 **Patient and transportation time associated with the background treatments applied in the advanced disease stages**

	Total patient time	Treatments per cycle
Brentuximab vedotin	1.5 hour	1.45
Gemcitabine	1.5 hour	3.26
ECP	1.5 hour	2.17

Source: Assumptions.

2.9 Sensitivity analyses

Due to the highly individualised treatment- and disease course of MF-CTCL, we identified several uncertainties in the model. To assess the impact of varying relevant parameters and assumptions on the result of the cost per patient analysis, we conducted several sensitivity analyses, which we present in the following. All sensitivity analyses were one-way analyses.

Sensitivity analyses on model assumptions

In the base case, response rates for the phototherapies were derived from the PROCLIPI registry. Phan et al. 2019 was an alternative option, and we assessed the impact on the result if response rates from Phan et al. 2019 were applied instead. Transitions between the three disease stages were derived from Agar et al. 2010 in the base case, and we conducted a sensitivity analysis where we applied data from Wernham et al. 2015 instead (19,26).

In the base case, the time horizon was set to be lifelong. To assess the impact of shorter time horizons on the cost per patient analysis, we conducted a sensitivity analysis, reducing the time horizon to 20 years.

To sum up, the following sensitivity analyses will be conducted on the model assumptions:

- response rates (CR and PR) for comparators with Phan et al. 2019; and
- disease stage transitions from Wernham et al. 2015;
- assessing for progression at the same timepoint for all alternatives (three months); and
- reduced time horizon: 20 years.

Sensitivity analyses of resource use

In the base case, we assumed the same daily dose of 2.21 g chlormethine gel regardless of whether patients had low or high skin burden and what disease stage they were in. To assess the impact of assuming different daily doses between skin burdens, we applied a daily dose of 1.31 g for patients with low skin burden (stage IA and 15% of patients in IIB+) and a daily dose of 3.46 g for patients with high skin burden (stage IB/IIA and %85 in IIB+). Moreover, as mentioned in section 1.1, the administration frequency can be varied and is in general very individualised. In the base case, we assume that patients administer chlormethine gel once daily. To assess the impact of other administration frequencies on the result of the cost per patient analysis, we conducted sensitivity analyses with an administration frequency of chlormethine gel 3.44 times per week (applying the 2.21 g daily application). The frequency of 3.44 doses per week came from a French temporary use authorisation (ATU) early access program.

To investigate the uncertainty in the cost per patient of PUVA, a sensitivity analysis was conducted assuming three treatments per week instead of two per week.

To sum up, the following sensitivity analyses will be conducted on the resource use:

- different daily chlormethine dose for low and high skin burden patients;
- administration frequency of chlormethine gel of 3.44 times weekly;
- number of PUVA treatments.

2.10 Overview of base case settings in the model

Table 35 **Overview of the base case settings and possible alternative settings in the model**

	Base case setting	Alternative setting options
Cost per patient analysis		
Applied model	Cohort Markov model	None
Patient population	Clinical question 1: Early stages (IA/IIA)	All stages Stage 1A only Late stages (IIB+)
Intervention	Chlormethine 0.02% gel	None
Comparator(s)	Narrowband UV-B and PUVA	None
Time horizon	Lifetime	Flexible
Discount rate	Year 2-35: 3.5% Year 36-70: 2.5%	The model is flexible for the user to outline other discounting rates.
Perspective	Limited societal	None
Included costs	Drug costs Hospital costs End-of-life costs Patient and transportation costs Adverse event costs	None
Subsequent treatments	Included	None
Background treatments for underlying disease	Included	None
Disease stage transitions	Agar et al. 2010	Wernham et al. 2015
Health state transitions	Chlormethine gel: Study 201, Kim et al. 2003 and expert opinion Comparators: PROCLIPI registry, Phan et al. 2019 and Whittaker et al. 2012	Chlormethine gel: None. Comparators: Phan et al. 2019
Initial timepoint for assessing progression	Chlormethine gel: 6 months PUVA: 2 months Narrowband UV-B: 3 months	Flexible
Inclusion of waste	No	None
Budget impact analysis		
Prevalence	275 patients	Flexible
Incidence	30 new patients each year	Flexible
Market shares	Year 1: 5% Year 2: 10% Year 3: 15% Year 4: 17% Year 5: 18%	Flexible

3 Results: Cost per patient analysis

In this section, we present the result of the cost per patient analysis in clinical question 1. We will not present any cost per patient results for clinical question 2 due to lack of data in the patient population specified in clinical question 2. However, we assume that the cost per patient in clinical question 2 will not differ substantially from the cost per patient in clinical question 1.

3.1 Result of the base case analysis

The incremental cost of treating adult patients with early stages of MF-CTCL with chlormethine gel compared to PUVA is DKK – 302,438 over a lifetime time horizon.

The incremental cost of treating adult patients with early stages of MF-CTCL with chlormethine gel compared to narrowband UV-B is DKK -329,144 over a lifetime time horizon.

The results of the cost per patient analysis of chlormethine gel compared to PUVA and narrowband UV-B are presented in Table 36 and Table 37, respectively.

Table 36 **Result of the cost per patient analysis of chlormethine gel compared to PUVA over a lifetime, in clinical question 1, discounted costs (DKK)**

	Chlormethine gel	PUVA	Incremental cost
Drug costs (incl. patient and transportation costs)	2,187,782	49,630	2,138,153
Hospital costs (incl. patient and transportation costs)	199,944	2,646,984	-2,447,041
End-of-life costs	23,354	23,354	0
Adverse event costs	6,450	0	6,450
In total	**2,417,530**	**2,719,968**	**-302,438**

Note: Since patient and transportation costs were not originally included in the global CU model, we had to include them by adding them to the markov traces of the cost elements to which they were incurred. Therefore, patient and transportation costs cannot be reported seperatly in this table.

Note: The cost per patient of chlormethine gel differs between Table 36 and Table 37 because, in the base case analysis, 20% of patients in the 'SDT health state' for chlormethine gel receive phototherapy. The difference is caused by the two different types of photptherapy: PUVA (Table 36) and UV-B (Table 37). Se further explanation in section 2.1.4.

Table 37 **Result of the cost per patient analysis of chlormethine gel compared to narrowband UV-B over a lifetime, discounted costs (DKK)**

	Chlormethine gel	Narrowband UV-B	Incremental cost
Drug costs (incl. patient and transportation costs)	2,225,581	43,145	2,182,436
Hospital costs (incl. patient and transportation costs)	199,944	2,717,440	-2,517,496
Cross sectional and end of life costs	23,354	23,354	0
Adverse event costs	5,916	0	5,916
In total	**2,454,795**	**2,783,939**	**-329,144**

Note: Since patient and transportation costs were not originally included in the global CU model, we had to include them by adding them to the markov traces of the cost elements to which they were incurred. Therefore, patient and transportation costs cannot be reported seperatly in this table.

Note: The cost per patient of chlormethine gel differs between Table 36 and Table 37 because, in the base case analysis, 20% of patients in the 'SDT health state' for chlormethine gel receive phototherapy. The difference is caused by the two different types of photptherapy: PUVA (Table 36) and UV-B (Table 37). Se further explanation in section 2.1.4.

3.2 Results of the sensitivity analyses

In this section, we present the results of the sensitivity analyses described in section 2.9. The developed Excel model does not contain a separate section with sensitivity analyses. Instead, the model includes the possibility to perform sensitivity analyses by changing the inputs and assumptions manually. Table 38, shows the results of the sensitivity analysis performed in the Excel model. For further analyses the model parameters can be changed in the Excel model. As seen in Table 38, the inputs with the largest impact on the result of the cost per patient analysis are the dose frequency of chlormethine gel and when response rates from Phan et al. 2019 are used instead of the PROCLIPI registry.

Table 38 **Results of the sensitivity analyses on the model assumptions**

	Incremental costs of chlormethine gel	
	PUVA	**Narrowband UV-B**
Base case incremental costs	**-302,438**	**-329,144**
Response rates from Phan et al. 2019	382,244	-49,861
Disease stage transitions from Wernham et al. 2015	-193,817	-238,859
20-year time horizon	-207,951	-291,386
Different daily chlormethine dose for low and high skin burden patients	-228,006	-273,600
Dose frequency of chlormethine gel 3.44 times per week	-1,231,423	-1,181,307
PUVA treatment three times per week	-306,227	-

4 Methods: budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending chlormethine gel as the standard treatment of MF-CTCL at the Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of chlormethine gel. The budget impact analysis compares the costs for the Danish regions in the scenario where chlormethine gel is recommended as a possible standard treatment and the scenario where chlormethine gel is not recommended as a possible standard treatment of MF-CTCL. The total budget impact per year is the difference between the two scenarios. The costs in the budget impact analysis are based on the cost per patient analysis but exclude patient and transportation costs and apply undiscounted costs.

The general methodology of the budget impact analysis is to multiply the estimated cost per patient of the included treatment alternatives in each year with the number of patients in the populations stated by the DMC protocol, adjusted for an assumed market share each year in the budget impact analysis (patient uptake) (1). To estimate the budget impact each year from year 1 to year 5, we calculated the average cost per patient of the alternatives over the five years and multiplied it with the number of patients in the respective year.

4.1 Market share

If chlormethine gel is recommended as standard treatment, we assume an increasing uptake over the five years, starting with 5% in year 1 and ending with a market share (or patient uptake) of 18% in year 5, as seen in Table 39.

Table 39 **Market share each year in the budget impact analysis**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	5%	10%	15%	17%	18%
Not recommended	0%	0%	0%	0%	0%

Source: Assumption.

4.2 Patient numbers

The DMC expert committee estimates a prevalence of 250-300 MF-CTCL patients who would be candidates for treatment with chlormethine gel and a yearly incidence of 30 new patients (1).

We applied a patient number of 275 in the budget impact analysis, which is the average of the 250-300 patients. We assume that all patients will stay in the model for all five years.

The estimated number of patients treated with chlormethine gel and the comparators per year with recommendation is presented in Table 40, and the estimated number of patients treated with chlormethine gel and comparators each year if chlormethine gel is not recommended is presented in Table 41.

Table 40 **Number of patients treated with chlormethine gel and comparators each year in the budget impact analysis, if chlormethine gel is recommended**

	Year 1	Year 2	Year 3	Year 4	Year 5
Chlormethine gel	14	31	50	62	71
Comparators*	261	274	285	303	324

Source: Own calculations.
Please note that patient numbers are rounded.
*We assume that all patients in the comparator group receive either PUVA or narrowband UV-B.

Table 41 **Number of patients treated with chlormethine gel and comparators each year in the budget impact analysis, if chlormethine gel is not recommended**

	Year 1	Year 2	Year 3	Year 4	Year 5
Chlormethine gel	0	0	0	0	0
Comparators*	275	305	335	365	395

Source: Own calculations.
Please note that patient numbers are rounded.
*We assume that all patients in the comparator group receive either PUVA or narrowband UV-B.

4.3 Sensitivity analyses on the budget impact analysis

We conducted a sensitivity analysis of the incidence used in the budget impact analysis. Instead of assuming an incidence of 30 new patients per year, we assumed 15 new patients per year.

5 Results: budget impact analysis

In this section, we present the results of the budget impact analysis in the first five years with and without a recommendation of chlormethine gel. Results for chlormethine gel compared to PUVA and narrowband UV-B are presented separately.

Chlormethine gel compared to PUVA

The budget impact of recommending chlormethine gel as standard treatment is 524,576 DKK the first year and 2,660,352 DKK in year 5. The budget impact in each year can be seen in Table 42.

Table 42 **The budget impact each year with recommendation of chlormethine gel and without recommendation (PUVA as standard treatment), undiscounted DKK**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	40,544,884	45,547,721	50,625,498	55,440,987	60,144,066
Without recommendation	40,020,307	44,386,159	48,752,010	53,117,862	57,483,714
Budget impact	**524,576**	**1,161,562**	**1,873,487**	**2,323,124**	**2,660,352**

Chlormethine gel compared to narrowband UV-B

The budget impact of recommending chlormethine gel as standard treatment is – 8,399 DKK the first year and – 42,595 DKK in year 5. The budget impact in each year can be seen in Table 43.

Table 43 **The budget impact each year with recommendation of chlormethine gel as standard treatment and without recommendation (narrowband UV-B as standard treatment), undiscounted DKK**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	50,339,041	55,821,291	61,302,340	66,787,589	72,274,638
Without recommendation	50,347,440	55,839,888	61,332,336	66,824,785	72,317,233
Budget impact	**-8,399**	**-18,598**	**-29,996**	**-37,195**	**-42,595**

5.1 Results of the sensitivity analysis of the budget impact

The budget impact of chlormethine gel compared to PUVA in year 5 changed from 2,660,352 DKK to 2,248,185 DKK, when a yearly incidence of 15 new patients was applied instead of 30 patients.

The budget impact of chlormethine gel compared to narrowband UV-B in year 5 changed from -42,595 DKK to -35,996 DKK, when a yearly incidence of 15 new patients was applied instead of 30 patients.

6 Discussion

The cost per patient analyses showed that the incremental cost of chlormethine gel is DKK -302,438 compared to PUVA and DKK -329,144 compared to narrowband UV-B.

Modelling treatments for MF-CTCL is challenging due to the highly patient individualised treatment and disease course of MF-CTCL. To be transparent regarding the uncertainties in the cost per patient analysis, we conducted various sensitivity analyses. These analyses showed that the parameter that affects the result of the cost per patient the most is the dosing frequency of chlormethine gel. Moreover, applying the response rates from Phan et al. 2019 instead of the PROCLIPI registry also had a great impact on the result. Changing the yearly incidence of new patients from 30 to 15 did not have a significant impact on any of the budget impact analyses.

The cost per patient analysis was limited due to lack of data in the patient population specified in the protocol, especially the analysis of corticosteroids. Due to the lack of data on corticosteroids a comparison was not possible. According to the BAD guidelines, there is little evidence for the efficacy of corticosteroids in MF-CTCL (7). The guidelines acknowledge that topical corticosteroids, particularly very potent compounds, are effective for patches and plaques in some early stage (IA/IB) patients, but also state that responses are rarely complete nor enduring. Noticeably, topical corticosteroids are not considered 'MF-CTCL-specific' treatments by clinicians and are very frequently prescribed to patients prior to diagnosis of MF-CTCL in order to control the non-specific skin symptoms of inflammation and irritation that patients experience (and which clinicians often confuse with symptoms of other skin conditions, such as eczema and psoriasis). Corticosteroids used post-diagnosis are generally a concomitant therapy to manage the skin symptoms (e.g. pruritus) that may arise from treatments used for MF-CTCL, rather than as a viable alternative to the use of MF-CTCL treatments. In addition, according to the Danish clinical expert it is difficult to compare corticosteroids directly with chlormethine gel.

Currently, nitrogen mustard (chlormethine) is a treatment alternative for MF-CTCL patients in Danish hospitals, however, this will soon be unavailable. Chlormethine gel (Ledaga) could meet this unmet treatment need, especially as a treatment alternative for lesions where corticosteroids or phototherapy are no desirable alternatives (e.g. areas around the eyes, genitals, unnecessary exposure to phototherapy in view of secondary malignancy risk, hampered access to photobiology units etc.).

According to the Danish clinical expert, Danish MF-CTCL patients circulate between treatments and the clinical presentation is heterogeneous, requiring a patient-individual treatment approach. Thus, more treatment alternatives such as chlormethine gel would benefit the patients who suffer from MF-CTCL.

As mentioned, we were not able to identify any evidence suitable for answering clinical question 2. However, we believe that the results and benefits of chlormethine gel will be very similar in the patient population specified in clinical question 2, as no data suggest that patients with

patches and plaques in the head/neck region or genitals respond differently to treatment than patients with patches and plaques in other locations.

References

1. Medicinrådet. Medicinrådets protocol for vurdering af chlormethin til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides [Internet]. Medicinrådet; 2020. Available from: https://medicinraadet.dk/media/l32g0p12/medicinr%C3%A5dets-protokol-for-vurdering-af-chlormethin-til-topikal-behandling-af-mycosis-fungoides_adlegacy.pdf

2. Genetics Home Reference. Mycosis fungoides [Internet]. National Library of Medicine. [cited 2020 May 1]. Available from: https://ghr.nlm.nih.gov/condition/mycosis-fungoides

3. Kim E, Richardson S. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest. 2005;

4. Demierre M-F, Tien A. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. Arch Dermatol. 2015;

5. Lægehåndbogen. Mycosis fungoides [Internet]. Sundhed.dk. 2016 [cited 2020 Apr 29]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hud/tilstande-og-sygdomme/skaellende-hudlidelser/mycosis-fungoides/

6. Wong H, Mishra A, Hake T. Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol. 2011;

7. Gilson D, Whittaker S. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Supplementary Information. Br J Dermatol 2019. 2018;

8. Demierre M-F, Gan S. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Natl Cutan Lymphoma Found Surv. 2006;

9. Hodak E, Lessin SR, Friedland R. New insights into associated co-morbidities in patients with cutaneous T-cell lymphoma (mycosis fungoides). Acta DermVenereol. 2013;

10. Olsen E, Vonderheid E, Pimpinelli N. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Ca. Blood. 2007;

11. Kempf W, Pfaltz K. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;

12. Willemze R, Hodak E. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29.

13. European Medicines Agenc. Summary of product characteristics: Ledaga [Internet]. European Medicines Agency; 2019 Last updated in [cited 2020 Nov 18]. Available from: https://www.ema.europa.eu/en/documents/product-information/ledaga-epar-product-information_en.pdf

14. Vonderheid EC. Topical mechlorethamine chemotherapy. Considerations on its use in mycosis fungoides. Int J Dermatol. 1984;

15. Beneton DD, Laribi K. Management of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL): focus on chlormethine gel. Cancer Manag Res. 2019;

16. Dronkert M, Kanaar R. Repair of DNA interstrand cross-links. Mutat Res. 2001;

17. Osawa T, Davies D. Mechanism of cell death resulting from DNA interstrand cross-linking in mammalian cells. Cell Death Dis. 2011;

18. Kevin Phan, Vignesh Ramachandran. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019;155:269–404.

19. Agar N, Wedgeworth E, Crichton E. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;

20. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, et al. Topical Chemotherapy in Cutaneous T-cell Lymphoma: Positive Results of a Randomized, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02%, Gel in Mycosis Fungoides. JAMA Dermatol. 2013 Jan 1;149(1):25.

21. Region Sjælland SU i R. PUVA lysbehandling [Internet]. Sjællands Universitetshospital i Roskilde; [cited 2020 Dec 10]. Available from: https://www.regionsjaelland.dk/sundhed/geo/roskildesygehus/Afdelinger/dermatologisk-afdeling/hudsygdomme/Lysbehandling/Sider/PUVA-lysbehandling.aspx

22. Hospitalsenhed Midt RV. Tablet PUVA-behandling [Internet]. Region midtjylland; [cited 2020 Dec 10]. Available from: https://www.hospitalsenhedmidt.dk/patientvejledninger/medicinsk-afdeling/tablet-puva-behandling/

23. University hospital of Northern Zealand. UVB treatment. Region of Northern Zealand; UVB.

24. Kim Y, Liu H, Mraz-Gernhard S. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003;

25. Whittaker S, Ortiz P. Efficacy and safety of bexarotene combined with psoralen– ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB–IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial 21011 (NCT00056056). Br J Dermatol. 2012;167.

26. Wernham AG, Shah F. Stage I mycosis fungoides: frequent association with a favourable prognosis but disease progression and disease-specific mortality may occur. Br J Dermatol. 2015;173.

27. Kim E, Geskin L. Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study. Abstr Eur J Cancer. 2019;

28. National Health Service (NHS). Health Survey for England 2017: Adult Health. [Internet]. National Health Service; [cited 2020 Dec 15]. Available from: https://files.digital.nhs.uk/75/9C8B99/HSE17-Adult-health-rep-v2.pdf

29. Medicinrådet. Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren. 2020. Report No.: Version 1.5.

30. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente – 2021 [Internet]. 2021. Available from: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf

31. European Medicines Agency. Summary of product characteristics: bexarotene (Targretin). [Internet]. European Medicines Agency; [cited 2020 Dec 11]. Available from: https://www.ema.europa.eu/en/documents/product-information/targretin-epar-product-information_en.pdf

32. Natalie Spaccarelli. The Use of Interferons in the Treatment of Cu taneous T-Cell Lymphoma. Dermatol Clin. 2015 Oct;33(4):731–45.

33. Pro.medicin. Gemcitabin 'Sandoz' [Internet]. pro.medicin.dk; [cited 2020 Dec 11]. Available from: https://pro.medicin.dk/Medicin/Praeparater/7398

34. European Medicines Agency. Summary of product characteristics: brentuximab vedotin. [Internet]. European Medicines Agency; [cited 2020 Dec 11]. Available from: https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_da.pdf

35. Medicinrådet. Værdisætning af enhedsomkostninger. 2020. Report No.: Version 1.3.

Medicinrådet

Medicinrådets protokol for vurdering af chlormethin til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides

Versionsnr.: 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metode, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

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Indhold

1 Begreber og forkortelser

CAILS	*Composite Assessment of Index Lesion Severity*
CI	Konfidensinterval
CR	Komplet respons
CT	Computer tomografi
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
ITT	*Intention to treat*
KTCL	Kutant T-cellelymfom
MF	Mycosis fungoides
mSWAT	Modificeret *Severity Weighted Assessment Tool*
OR	*Odds ratio*
PD	Progressiv sygdom
PD-1	*Programmed cell death protein 1*
PET	Positron-emissionstomografi
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
PR	Partiel respons
PUVA	8-methoxypsoralen + UV-A
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*
TNMB-system	*Tumor-, node-, metastasis-, blood-system*
UV-A	Ultraviolet lys type A
UV-B	Ultraviolet lys type B

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Recordati Rare Diseases og Helsinn Birex Pharmaceuticals Ltd., som ønsker, at Medicinrådet vurderer chlormethin til topikal behandling af kutant T-cellelymfom af typen mycosis fungoides (MF). Medicinrådet modtog den foreløbige ansøgning den 24. juni 2020.

2.1 Mycosis fungoides

MF er den hyppigste form af alle kutane T-cellelymfomer (KTCL). KTCL er en heterogen gruppe af sjældne non-Hodgkin-lymfomer, hvor MF udgør omkring 50-60 %. Medianalder ved diagnose er typisk 55-60 år med overvægt af mænd. MF viser sig i form af erythematøse patches, plaques og, sjældnere, tumorer i huden og er almindeligvis langsomt progredierende [1]. MF ses meget sjældent med blodinvolvering. Patienterne er plagede af deres hudsymptomer, som har stor indflydelse på livskvaliteten. Forandringerne i huden og den medfølgende immunhæmmende behandling gør patienterne udsatte for infektioner, der kan udvikle sig til blodforgiftning (sepsis), som er livstruende. Hos nogle patienter optræder der behandlingsresistente patches eller plaques og/eller patches eller plaques i hoved-/halsregionen eller kønsdelene, som kan være særligt generende.

MF inddeles efter et tumor-, node-, metastases-, blod-(TNMB) system i stadier fra I-IV efter *International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer's* reviderede kriterier [2]. Stadieinddelingen omfatter normalt blodprøver, en PET-/CT-skanning og en knoglemarvsundersøgelse. Stadierne er forklaret i tabel 1.

Tabel 1. Stadieinddeling for MF

Stadie		
IA	Stadie 1A betyder, at mindre end 10 % af huden er involveret.	Lymfomet er begrænset til huden (patches eller plaque).
IB	Stadie 1B betyder, at 10 % eller mere af huden er involveret.	
IIA	Stadie 2A betyder, at der er patches eller plaque på huden, og lymfeknuderne er forstørrede, men de indeholder ikke unormale lymfomceller.	
IIB	Stadie 2B betyder, at der er en eller flere forhøjede tumorer i huden. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.	
IIIA	Stadie 3A betyder, at der er få eller ingen lymfomceller i blodbanen (erythrodermisk mycosis fungoides).	80 % eller mere af huden er involveret med erythrodermi (diffus rødme, fortykkelse og eventuelt sprækker i huden), hævelse, kløe og undertiden smerte. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.
IIIB	Stadie 3B betyder, at et moderat antal lymfomceller findes i blodbanen.	
IVA	Stadie 4A betyder, at der er talrige unormale lymfomceller i blodbanen (Sézarys syndrom), eller lymfeknuderne indeholder lymfomceller. Der er lymfom i huden i form af patches, plaques og/eller erythrodermi.	
IVB	Stadie 4B betyder, at lymfomet er spredt til andre organer.	

Prognosen for MF er stadieafhængig. Stadie IA og IB har en god prognose. Hos velbehandlede patienter er der rapporteret medianoverlevelse på 35,5 år, 21,5 år og 15,8 år for henholdsvis stadie IA, IB og IIA [3]. Omtrent 25 % af patienterne med stadie IA eller IB oplever med tiden progression til mere avancerede sygdomsstadier. Stadie IIB og III har en medianoverlevelse på 4-6 år, mens stadie IV har en

medianoverlevelse på mindre end 4 år. Sygdommen har således et meget varierende forløb med meget forskellig restlevetid. Indtræder der progressiv sygdom, f.eks. når der kan detekteres maligne celler i blodet, forringes prognosen markant [3].

I Danmark lever ca. 400-500 patienter med behandlingskrævende KTCL (lokal såvel som systemisk behandling), hvor ca. 60 % af patienterne har MF. Fagudvalget vurderer derfor, at der er ca. 250-300 patienter med MF, der er kandidater til chlormethin (prævalens), og at der vil være ca. 30 nye patienter om året (incidens).

2.2 Chlormethin

Chlormethin er et celledræbende (alkylerende) middel, der hæmmer hurtigt delende celler og påbegynder en proces, hvor celler ødelægger sig selv – også kaldet programmeret celledød (apoptose).

Chlormethin kendes også under navnene mechlorethamin og kvælstof-sennepsgas. Det markedsføres som en gel under handelsnavnet Ledaga. Gelen på 60 g indeholder 0,02 % chlormethin svarende til 160 µg/g. Gelen påføres i et tyndt lag på de afficerede hudområder én gang dagligt. Behandlingen forventes at blive initieret med en lavere administrationsfrekvens, f.eks. tre gange ugentlig, hvorefter dosis optitreres til én gang dagligt. Når der opnås et tilfredsstillende respons, vil dosis blive forsøgt reduceret ved gradvist at øge administrationsintervallerne til en vedligeholdelsesdosis på f.eks. én gang ugentligt eller hver anden uge. Det kan blive nødvendigt løbende at justere administrationsfrekvens afhængigt af tolerabilitet.

Ved alvorlige hudreaktioner på det behandlede område afbrydes behandlingsforløbet. Behandling genoptages ved bedring af symptomer hver 3. dag i en uge, herefter hver 2. dag i en uge og herefter én gang dagligt.

Behandlingsvarigheden vil være individuel, og behandlingen fortsættes, så længe der er et tilfredsstillende respons, og behandlingen er veltolereret.

Chlormethin-gel er indiceret til behandling af KTCL af typen MF og kan dermed anvendes som topikal behandling på tværs sygdomsstadier alene eller i kombination med andre behandlinger. Det blev godkendt af EMA d. 3. marts 2017 og har status som et lægemiddel til sjældne sygdomme (*orphan medicinal product*).

2.3 Nuværende behandling

Behandlingen af kutant T-cellelymfom i Danmark varetages af de dermatologiske afdelinger i samarbejde med hæmatologiske og onkologiske afdelinger. Behandlingen følger internationale guidelines fra *European Society for Medical Oncology* og *European Organisation for Research and Treatment of Cancer* [4,5]. Der er ingen defineret standardbehandling, da behandlingen individualiseres ud fra det kutane lymfoms karakteristika, sygdommens sværhedsgrad, patientens performancestatus, komorbiditeter, tidligere behandlinger, patientens præferencer mv.

Målet med behandlingen er sygdomskontrol, forbedring af livskvalitet og symptomlindring, idet behandlingen, fraset allogen stamcelletransplantation, ikke er kurativ. Først forsøges tumorbyrden nedbragt, hvorefter sygdommen kontrolleres og følges. Den palliative strategi går således ud på at lindre symptomer, inducere remissioner, udskyde progression og undgå betydelig behandlingsrelateret toksicitet. Behandlingsforløbene er oftest af længere varighed (år).

I tidlige stadier af MF (IA-IIA) anvendes topikal behandling i form af f.eks. kortikosteroider i kombination med ultraviolet lysbehandling (smalspektret UVB eller 8-methoxypsoralen + UV-A (PUVA)) eller penslinger med kvælstof-sennepsgas.

Selvom responsraterne ofte er gode ved de nuværende topikale behandlinger, har de også visse begrænsninger. Det gælder f.eks. lysbehandling, hvor antallet af behandlinger er begrænset af den

kumulative uv-dosis, og ved kortikosteroider, hvor længerevarende behandling kan føre til atrofi i forskellige hudlag (dermis og epidermis). Derfor er der også et behov for alternative behandlingsmuligheder.

Når sygdommens udbredelse er begrænset til huden, cirkulerer patienterne mellem de forskellige topikale behandlinger. Rækkefølgen kan variere fra patient til patient, fælles gælder dog, at kortikosteroider ofte forsøges som den initiale topikale behandling. Gentagne behandlinger med samme lægemiddel er ikke usædvanligt (dette forventes også at gælde chlormethin), og i praksis vil lysbehandling kunne følges af chlormethin eller omvendt. I Danmark varetages den specialiserede behandling på Aarhus Universitetshospital og på Bispebjerg Hospital. Penslinger med kvælstof-sennepsgas tilbydes kun på Aarhus Universitetshospital, mens man på Bispebjerg Hospital har tradition for hyppigere at bruge PUVA sammenlignet med Aarhus. Derfor kan det også forekomme, at patienter modtager behandling i en anden region, hvis dette vurderes at være den bedste løsning for patienten. Brug af penslinger med kvælstof-sennepsgas vil ophøre inden for en overskuelig tid, da det ikke længere kan skaffes. Derfor betragtes det ikke som standardbehandling.

Normalt fortsætter brugen af forskellige topikale behandlinger, indtil der ikke længere opleves en tilstrækkelig bedring af patientens symptomer, eller de ikke længere tolereres. De anvendes derfor også ofte i kombination med systemisk medicinsk behandling.

I senere, mere fremskredne stadier (IIB-IV) af MF anvendes lavdosis elektronvolts-helkropsbestråling, lokal strålebehandling mod tumor eller systemisk medicinsk behandling i form af interferon-α, retinoider (f.eks. acitretin og bexaroten) eller lavdosis-methotrexat. Til udvalgte få patienter kan anvendes knoglemarvstransplantation, som gives med kurativ intention. De forskellige former for systemisk behandling kombineres ofte og anvendes ofte også i kombination med topikale behandlinger og/eller ultraviolet lysbehandling. Behandlingen, der følger efter de første systemiske behandlinger (interferon-α, retinoider, lavdosis-methotrexat) planlægges ved multidisciplinær konference med hæmatologisk afdeling, og der anvendes targeterede behandlinger, pathway-hæmmere eller kemoterapi (f.eks. højdosis-methotrexat, gemcitabin eller doxorubicin).

De targeterede behandlinger omfatter brentuximab vedotin (anti-CD30), og alemtuzumab (anti-CD52) samt pembrolizumab (PD-1-hæmmer). Pathway-hæmmere omfatter histone deacetylase-hæmmeren romidepsin. Disse lægemidler betragtes af fagudvalget som ligeværdige behandlingsalternativer. Behandlingsvalget er individualiseret og guides af patientens markørudtryk. Ingen af de targeterede behandlinger/pathway-hæmmere kan betragtes som standardbehandlinger i Danmark, og kun brentuximab vedotin har indikation til behandling af KTCL. Behandlingen med disse alternativer er derfor afhængig af individuelle ansøgninger til lægemiddelkomitéerne. Det Europæiske Lægemiddelagentur (EMA) har tidligere afvist at give markedsføringstilladelse til romidepsin til denne indikation. Behandling med romidepsin er derfor ligesom pembrolizumab og alemtuzumab uden for godkendt indikation (off-label).

I dermatologien anvendes off-label-behandling i ganske stort omfang pga. manglende evidens for behandling til givne hudsygdomme.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne patienter med tidlige stadier af MF (I-IIA), som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling?

Population
Voksne patienter med tidlige stadier af MF (I-IIA), som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling.

Intervention
Chlormethin-gel 0,02 % appliceret én gang dagligt.

Komparator
Topikale kortikosteroider. Initialt appliceret én gang dagligt indtil overbevisende bedring, hvorefter behandlingen vedligeholdes ved applikation to gange om ugen.

Smalspektret UVB. Behandlingen gives typisk 3 gange ugentligt til effekt. Ofte gives der ca. 20-30 behandlinger pr. lyskur. UVB kan evt. anvendes som vedligeholdelsesbehandling med 1-2 behandlinger pr. uge over en længerevarende periode. For at undgå at inducere hudkræft stiles der mod maksimalt 250 behandlinger på en livstid.

8-methoxypsoralen + UV-A (PUVA). 8-methoxypsoralen doseres efter vægt: 40-49 kg: 20 mg; 50-69 kg: 30 mg; ≥ 70 kg: 40 mg. PUVA gives højst tre gange ugentligt. Typisk gives 20-30 behandlinger pr. behandlingskur. Behandlingen seponeres, når huden er afglattet. For at undgå at inducere hudkræft stiles der mod maksimalt 200 behandlinger på en livstid.

Effektmål
De valgte effektmål står i tabel 2.

3.2 Klinisk spørgsmål 2

Hvilken værdi har chlormethin sammenlignet med topikale kortikosteroider, smalspektret UVB og PUVA for voksne MF-patienter (stadie IIB-IV) eller voksne MF-patienter (uafhængigt af stadie) med patches eller plaques i hoved-/halsregionen eller på kønsdelene, som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling?

Population
Voksne MF-patienter (stadie IIB-IV) eller voksne MF-patienter (uafhængigt af stadie) med patches eller plaques i hoved-/hals regionen eller på kønsdelene, som har utilstrækkelig effekt af mindst én tidligere optimeret topikal behandling.

Intervention
Chlormethin-gel 0,02 % appliceret én gang dagligt eventuelt i kombination underliggende systemisk behandling.

Komparator
Topikale kortikosteroider. Initialt appliceret én gang dagligt indtil overbevisende bedring, hvorefter behandlingen vedligeholdes ved applikation to gange om ugen.

Smalspektret UVB. Behandlingen gives typisk tre gange ugentligt til effekt. Ofte gives der ca. 20-30 behandlinger pr. lyskur. UVB kan evt. anvendes som vedligeholdelsesbehandling med 1-2 behandlinger pr. uge over en længerevarende periode. For at undgå at inducere hudkræft stiles der mod maksimalt 250 behandlinger på en livstid.

8-methoxypsoralen + UV-A (PUVA). 8-methoxypsoralen doseres efter vægt: 40-49 kg: 20 mg; 50-69 kg: 30 mg; ≥ 70 kg: 40 mg. PUVA gives højst tre gange ugentligt. Typisk gives 20-30 behandlinger pr. behandlingskur. Behandlingen seponeres, når huden er afglattet. For at undgå at inducere hudkræft stiles der mod maksimalt 200 behandlinger på en livstid.

De valgte komparatorer gives eventuelt i kombination underliggende systemisk behandling.

Effektmål
De valgte effektmål står i tabel 2.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 2. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 2. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Reduktion af hudsymptomer	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel med respons (CR+PR) på mSWAT	15 %-point
Livskvalitet	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid Skindex-29 total score - fra baseline til endt opfølgning	10 point
			Andel patienter som opnår en 10-points reduktion i Skindex-29 total-score	*Der er ikke fastsat en mindste klinisk relevant forskel. Denne måleenhed anvendes til bestemmelse af den relative effektforskel.*
Varighed af respons	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Median varighed af respons	4 måneder
Bivirkninger	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter med uønskede hændelser grad 3-4	1 %-point
			Andel af patienter der oplever alvorlige uønskede hændelser (SAE'er)	1 %-point

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.3.1 Kritiske effektmål

Reduktion af hudsymptomer

Der findes flere validerede og internationalt anerkendte instrumenter til at vurdere behandlingseffekt på patienternes hudsymptomer. Både *Composite Assessment og Index Lesion Severity* (CAILS) og det modificerede *Severity Weighted Assessment Tool* (mSWAT) anbefales som relevante effektmål i kliniske

studier herunder i retningslinjerne: *International Society for Cutaneous Lymphomas (ISCL), US Cutaneous Lymphoma Consortium og EORTC Cutaneous Lymphoma Task Force Consensus* [6].

CAILS indeholder vurdering af udvalgte hudsymptomer som rødme (erytem), afskalning, plaquehøjde og hypopigmentering eller hyperpigmentering. Her udvælges op til 5 repræsentative indekslæsioner, som danner grundlag for effektvurderingen. De udvalgte læsioner vurderes løbende og respons opgøres i forhold til patientens tilstand ved baseline. CAILS egner sig godt til behandlinger som er målrettet mod visse, men ikke alle læsioner, eller hvor man ønsker at overvåge effekten af behandling til kun én type læsion.

MSWAT baserer sig i højere grad på en helhedsvurdering af hudtumorbyrden hos patienter med MF. Det anbefales og anvendes i vid udstrækning i kliniske studier. MSWAT måler det procentvise samlede overfladeareal (*total body-surface area*) med involvering for hhv. patches, plaques og tumorer. Tolv kropsområder vurderes, og overfladeareal for hver læsionstype multipliceres med et tal (patch = 1, plaque = 2; tumor = 4) og summeres for at bestemme den totale mSWAT-score. Et komplet respons (CR) kræver totalt fravær af hudlæsioner (100 % reduktion). Partiel respons (PR) kræver ≥ 50 % reduktion i mSWAT-score uden nyopståede tumorer sammenlignet med baseline. CR/PR bekræftes ved gentagen vurdering efter ≥ 4 uger. Stabil sygdom bliver defineret som mindre end 50 % reduktion til mindre end 25 % stigning i mSWAT-score uden nyopståede tumorer sammenlignet med baseline. Progressiv sygdom (PD) defineres som ≥ 25 % stigning i mSWAT-score fra baseline, herunder tab af respons hos patienter med CR eller PR.

Fagudvalget ønsker effektmålet opgjort som responsrate defineret som andelen af patienter med CR eller PR på MSWAT, også kaldet den samlede responsrate. MSWAT er valgt ud fra fagudvalgets direkte kendskab til dette instrument i forhold til CAILS. Som nævnt tidligere er responsraterne på de eksisterende behandlinger (kortikosteroider, UVB og PUVA) ofte gode i de tidlige stadier. I tidlige studier ligger den samlede responsrate mellem ca. 50-90 % [7–9]. Det er dog væsentligt at bemærke, at flere af de tidligere studier har anvendt mindre stringente kriterier for vurdering af respons. Derfor er det også fagudvalgets erfaring, at den samlede responsrate i dansk klinisk praksis i gennemsnit ligger på ca. 60 %. Den mindste klinisk relevante forskel fastsættes på denne baggrund til 15 %-point.

Livskvalitet

Livskvalitet fremhæves af fagudvalget som et yderst relevant effektmål, når patienterne lever længe med deres sygdom. Behandlingen er palliativ, og patienternes livskvalitet undervejs i behandlingen er derfor afgørende. I vurderingen af chlormethin vurderes livskvalitet som et kritisk effektmål. Patienternes livskvalitet er tæt forbundet med deres hudsymptomer, da hudgenerne medfører betydeligt ubehag for patienterne og samtidig en øget infektionsrisiko. Derfor ønskes livskvalitet vurderet ved Skindex-29. Skindex-29 er et selvrapporteret spørgeskema, der er udviklet til at måle dermatologisk specifik livskvalitet. Spørgeskemaet består af tre underskalaer: hudrelaterede, emotionelle og funktionelle symptomer. Den totale score går fra 29-116 og transformeres i vurderingen af livskvalitet til en lineær skala fra 0-100, hvor en højere score indikerer en dårligere livskvalitet [10]. Fagudvalget er ikke bekendt med studier, som undersøger mindste klinisk relevante forskelle for brugen af Skindex-29 hos patienter med KTCL. Værktøjet er imidlertid generisk i den forstand, at det er beregnet til brug for enhver form for hudlidelse. Der findes studier, som har forsøgt at fastsætte cut-off-værdier for henholdsvis mild, moderat og svær påvirkning af den samlede livskvalitet ved brug af Skindex-29 såvel som for de enkelte domæner (hudrelaterede, emotionelle og funktionelle symptomer). Her viser et studie, at en 10-pointsreduktion i totalscore svarer til en ændring fra svær til moderat påvirkning og tilsvarende fra moderat til mild påvirkning [11]. På denne baggrund har fagudvalget valgt 10 point som den mindste klinisk relevante forskel. Som supplement til den gennemsnitlige ændring i totalscore ønsker fagudvalget en opgørelse af effekten på de enkelte domæner med henblik på en kvalitativ vurdering af effekten på livskvalitet.

For at kunne vurdere den relative effektforskel ønsker fagudvalget en opgørelse af forskellen i andel patienter, som opnår en 10-pointsreduktion i Skindex-29 totalscore.

3.3.2 Vigtige effektmål

Varighed af respons
Varighed af respons defineres som tiden fra første bekræftet respons (CR eller PR ved mSWAT) til første evaluering, hvor responset ikke længere er til stede (PD er blevet dokumenteret). Dette er en vigtig parameter, da responsvarigheden er et udtryk for sygdomskontrol hos patienterne. Tiden til tilbagefald er meget varierende og vil dels afhænge af, hvilken behandling som gives, og om der gives vedligeholdelsesbehandling, efter der er induceret et respons. Baseret på tidligere studier anslås varighed af respons ved de topikale behandlinger at ligge mellem 6-32 måneder [12,13]. Dansk klinisk erfaring tilsiger, at responsvarigheden ligger i den lave ende af dette interval, da responsvurderingen i studierne, som omtalt tidligere, i mange tilfælde er baseret mindre stringente responskriterier. Derfor fastsættes den mindste klinisk relevante forskel til 4 måneder i den mediane varighed af respons.

Uønskede hændelser

Uønskede hændelser grad 3-4

Forekomsten af uønskede hændelser grad 3-4 har stor betydning for den enkelte patients livskvalitet og vilje til at forblive i en behandling over længere tid. Eventuelle bivirkninger skal tolereres over en lang periode. Ifølge fagudvalgets erfaring er frekvensen af uønskede hændelser grad 3-4 lav med de nuværende topikale behandlinger (ca. 1 %). Fagudvalget betragter en forskel på 1 %-point mellem patientgrupperne som den mindste klinisk relevante forskel.

Alvorlige uønskede hændelser (SAE'er)

Fagudvalget hæfter sig ved, at bivirkningsprofilen skal stå mål med lægemidlets effekt, især i betragtning af at der er tale om en pallierende behandling. Behandlingen bør derfor undgå at give betydelig alvorlig toksicitet. Ifølge fagudvalgets erfaring ses sjældent alvorlige uønskede hændelser med de nuværende topikale behandlinger (ca. 1 %). Fagudvalget betragter en forskel på 1 %-point mellem patientgrupperne som den mindste klinisk relevante forskel.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere studier, hvor chlormethin er sammenlignet direkte med en eller flere af de valgte komparatorer.

Medicinrådet har ikke fundet studier, der indeholder en direkte sammenligning. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere EMAs European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed https://www.ncbi.nlm.nih.gov/pubmed/advanced:

#	Søgetermer	Kommentarer
1	Lymphoma, T-Cell, Cutaneous[majr]	Termer for indikation
2	(MF-type[tiab] and CTCL[ti]) OR (cutaneous[ti] AND t-Cell[ti] AND lymphom*[ti]) OR (mycosis[ti] AND fungoides[ti])	
3	#1 OR #2	
4	Mechlorethamine[mh]	

5	mechlorethamin*[tiab] OR chlormethin*[tiab] OR Ledaga[tiab] OR Nitrogen mustard[tiab] OR Chlorethazin*[tiab] OR Mustine[tiab]	Termer for intervention og komparator
6	(Administration, Cutaneous[mh] OR Administration, Topical[mh]) AND (Adrenal Cortex Hormones[mh] OR Steroids[mh])	
7	corticosteroid*[tiab] OR hydrocortison*[tiab] OR cobadex[tiab] OR dioderm[tiab] OR efcortelan[tiab] OR hydrocortisyl[tiab] OR mildison[tiab] OR alphaderm[tiab] OR calmurid[tiab] OR locoid[tiab] OR alclometason*[tiab] OR modrasone[tiab] OR beclomethason*[tiab] OR beclometason*[tiab] OR propaderm[tiab] OR betamethason*[tiab] OR betametason*[tiab] OR betacap[tiab] OR betnovate[tiab] OR diprosone[tiab] OR diprosalic[tiab] OR bettamousse[tiab] OR clobetasol*[tiab] OR dermovate[tiab] OR clobetason*[tiab] OR eumovate[tiab] OR trimovate[tiab] OR desoxymethason*[tiab] OR desoximetason*[tiab] OR stiedex[tiab] OR diflucortolon*[tiab] OR nerison*[tiab] OR fluocinolon*[tiab] OR synalar[tiab] OR fluocinonid*[tiab] OR metosyn[tiab] OR fluocortolon*[tiab] OR ultralanum[tiab] OR flurandrenolon*[tiab] OR fludroxycortid*[tiab] OR haelan[tiab] OR fluticason*[tiab] OR cutivate[tiab] OR halcinonid*[tiab] OR halciderm[tiab] OR mometason*[tiab] OR elocon[tiab] OR triamcinolon*[tiab] OR adcortyl[tiab] OR aureocort[tiab] OR tri-adcortyl[tiab]	
8	Ultraviolet Therapy[majr]	
9	PUVA[tiab] OR ultraviolet[tiab] OR (psoralen[tiab] AND (UVA[tiab] OR ultraviolet-A[tiab])) OR UVB[tiab]	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	
11	#3 AND #10	Kombination af indikation, intervention og komparator
12	Animals[mh] NOT Humans [mh]	Eksklusion af ikke relevante studier og publikationstyper
13	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	
15	#12 OR #13 OR #14	
16	#11 NOT #15	**Endelig søgning**

Søgestreng til CENTRAL https://www.cochranelibrary.com/advanced-search/search-manager:

#	**Søgetermer**	**Kommentarer**
1	[mh "Lymphoma, T-Cell, Cutaneous"]	Termer for indikation
2	("mycosis fungoides" or "cutaneous T cell lymphoma"):kw	
3	MF-type:ti,ab and CTCL:ti	
4	(cutaneous near "t cell" near lymphom*):ti OR (mycosis near fungoides):ti	
5	#1 or #2 or #3 or #4	
6	(mechlorethamine or chlormethine):kw	Termer for intervention og komparator
7	(mechlorethamin* or chlormethin* or "nitrogen mustard" or chlorethazin* or Mustine):ti,ab	
8	[mh "Adrenal Cortex Hormones"]	
9	[mh Steroids]	
10	glucocorticoid:kw	
11	(corticosteroid* or hydrocortison* or cobadex or dioderm or efcortelan or hydrocortisyl or mildison or alphaderm or calmurid or locoid or alclometason or modrasone or beclomethason* or beclometason* or propaderm or betamethason* or betametason* or betacap or betnovate or diprosone or diprosalic or bettamousse or clobetasol* or dermovate or clobetason* or eumovate or trimovate or desoxymethason* or desoximetason* or stiedex or diflucortolon* or nerison* or fluocinolon* or synalar or fluocinonid* or metosyn or fluocortolon* or ultralanum or flurandrenolon* or fludroxycortid* or haelan or fluticason* or cutivate or halcinonid* or halciderm or mometason* or elocon or triamcinolon* or adcortyl or aureocort or tri-adcortyl):ti,ab,kw	
12	("ultraviolet therapy" or "ultraviolet phototherapy" or puva or "puva therapy"):kw	
13	(PUVA or ultraviolet or (psoralen AND (UVA or "ultraviolet A")) OR UVB):ti,ab	
14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	
15	#5 and #14	Kombination af indikation, intervention og komparator
16	("conference abstract" or review):pt	

17	NCT*:au	Eksklusion af ikke relevante publikationstyper
18	("clinicaltrial gov" or trialsearch):so	
19	(meeting or abstract or review):ti	
20	#16 or #17 or #18 or #19	
21	#15 not #20	**Endelig søgning** (begræns til Trials)

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.

- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'- og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

7.1 Behandlingsvarighed

Fagudvalget ønsker, at ansøger fremsender information om den forventede behandlingsvarighed med chlormethin.

7.2 Sundhedsøkonomiske analyser

Ansøger bedes inddrage sammenligninger med alle relevante komparatorer i de sundhedsøkonomiske analyser.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet.

9 Referencer

1. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer. 2017;77:57–74.
2. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Ca. Blood. 2007;110(6):1713–22.
3. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. J Clin Oncol. 2010;28(31):4730–9.
4. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118(15):4024–35.
5. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv30–40.
6. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the E. J Clin Oncol. 2011;29(18):2598–607.
7. Olsen EA, Hodak E, Anderson T, Carter JB, Henderson M, Cooper K, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol. 2016;74(1):27–58.
8. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides. JAMA Dermatology. 2019;155(3):335.
9. Tarabadkar ES, Shinohara MM. Skin Directed Therapy in Cutaneous T-Cell Lymphoma. Front Oncol. 2019;9.
10. Chren M-M. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin. 2012;30(2):231–6, xiii.
11. Prinsen CAC, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. J Invest Dermatol. 2011;131(9):1945–7.
12. Lovgren M-L, Scarisbrick JJ. Update on skin directed therapies in mycosis fungoides. Chinese Clin Oncol. 2019;8(1):7–7.
13. Nikolaou V, Sachlas A, Papadavid E, Economidi A, Karambidou K, Marinos L, et al. Phototherapy as a first-line treatment for early-stage mycosis fungoides: The results of a large retrospective analysis. Photodermatol Photoimmunol Photomed. 2018;34(5):307–13.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

Formand	**Indstillet af**
Lars Møller Pedersen Forskningsansvarlig overlæge	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Jakob Madsen Overlæge	Region Nordjylland
Paw Jensen Ledende overlæge	Region Nordjylland
Peter Kamper Overlæge, ph.d.	Region Midtjylland
Ida Blok Sillesen Afdelingslæge	Region Midtjylland
Jacob Haaber Christensen Overlæge, ph.d.	Region Syddanmark
Dorte Maegaard Tholstrup Afdelingslæge, ph.d.	Region Sjælland
Michael Pedersen Overlæge	Region Hovedstaden
Michael Boe Møller Overlæge	Dansk Patologiselskab
Kathrine Bruun Svan Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Jørn Søllingvrå Patient/patientrepræsentant	Danske Patienter
En patient/patientrepræsentant	Danske Patienter
Rikke Bech Afdelingslæge, ph.d.	Dansk Dermatologisk Selskab
Maria Rørbæk Kamstrup Reservelæge, ph.d.	Dansk Dermatologisk Selskab

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

11 Versionslog

Version	Dato	Ændring
1.0	05. okt. 2020	Godkendt af Medicinrådet.
1.1	04. nov. 2020	Præcisering af populationerne i de to kliniske spørgsmål.