15 December 2016
EMA/CHMP/13156/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LEDAGA

International non-proprietary name: chlormethine

Procedure No. EMEA/H/C/002826/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADP	adenosine diphosphate
ALT	alanine transaminase
AMM	Autorisation de Mise sur le Marché (Marketing authorization)
AST	aspartatetransaminase
ATP	adenosine triphosphate
AP	Aquaphor ointment
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CHMP	Committee for Medicinal Products for Human use
CTCL	cutaneous T-cell lymphoma
DD	daily (clinical) dose
DMSO	dimethyl sulfoxide
DMPK	drug metabolism and pharmacokinetics
DNA	deoxyribonucleic acid
DSC	Differential Scanning Calorimetry
DEGEE	diethylene glycol monoethyl ether
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
EU	European Union
FDA	United States Food and Drug Administration
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GD	gestation day
GLP	Good Laboratory Practice
GSH	glutathione
GSSG	glutathione disulfide
HED	human equivalent dose
HP	highly purified
HPRT	hypoxanthine-guanine phosphoribosyltransferase
IARC	International Agency for Research on Cancer
IC50	half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IID	Inactive Ingredient Database
i.p.	intraperitoneal
i.v.	intravenous
IR	InfraredKF Karl Fischer titration
LD50	median lethal dose
MDA	malondialdehyde
MDEA	N-methyldiethanolamine
MF	mycosis fungoides
MF-type CTC	mycosis fungoides-type cutaneous T-cell lymphoma
MNNG	N-methyl-N´-nitro-N-nitrosoguanidine
MTD	maximum tolerated dose
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
NF	National Formulary
NM	nitrogen mustard
NMR	Nuclear Magnetic Resonance
NOAEL	no-observed-adverse-effect level
PARP	poly(ADP-ribose) polymerase
PEG	polyethylene glycol
PG	propylene glycol ointment
Ph. Eur.	European Pharmacopoeia
RBC	red blood cells
RH	Relative Humidity
RNA	ribonucleic acid
RRT	relative retention time
s.c.	subcutaneous

SEM	standard error of the mean
SWAT	Severity Weighted Assessment Tool
TLT	Treatment limiting toxicity
UV	ultraviolet
WBC	white blood cells
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actelion Registration Ltd. submitted on 17 April 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Ledaga (chlormethine gel), through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2012.

The application concerns a hybrid medicinal product and refers to a reference product, as defined in Article 10(2)(b) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

Chlormethine gel, was designated as an orphan medicinal product EU/3/12/963 on 22 May 2012 for the following indication: Treatment of cutaneous T-cell lymphoma.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Caryolysine, 0.16%, Concentrate and solvent for solution for injection and concentrate and solvent for cutaneous solution.
- Marketing authorisation holder: PRIMIUS LAB LIMITED
- Date of authorisation: 02-06-1946
- Marketing authorisation granted by:
  - Member State (EEA) : FR
    - National procedure
- Marketing authorisation number:301 912.9 (1949/97 rev 1999)
- Chlormethine gel was approved as Valchlor in the US in August 2013 for the topical treatment of Stage IA and IB mycosis fungoides - type cutaneous T - cell lymphoma in patients who have received prior skin - directed therapyMF.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ledaga as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice / Protocol assistance

The applicant did not seek scientific advice or protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Sinan B. Sarac

- The application was received by the EMA on 17 April 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 4 September 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2016.
- The Rapporteur circulated the joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 22 August 2016.
- The Rapporteur circulated an updated joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a consolidated list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 15 November 2016.
- The Rapporteur circulated the joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 30 November 2016.

- The Rapporteur circulated an updated joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 December 2016.
- During the meeting on 12-15 December 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Ledaga on 15 December 2016.

2. Scientific discussion

2.1. Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of lymphoproliferative diseases characterised by infiltration of the skin by malignant T-cells. The epidermotropic form of CTCL is the most common and is referred to as mycosis fungoides (MF), accounting for 60% of new CTCL cases. CTCL is a rare type of tumour and the RARECARE cancer[1] registry reports a combined incidence rate of 0.52/100,000 for MF-type CTCL and the more aggressive Sézary Syndrome. It is estimated that the 5-year partial prevalence of MF-type CTCL is 11,735 in EU-28 countries[2]. Overall survival as well as disease-specific survival decrease with advancing clinical stage. In treated patients, median survival with early stage disease (Stage IA, IB and IIA) is reported as 35.5, 21.5 and 15.8 years, respectively[3]. The prognosis for patients with MF-type CTCL is worse when the condition is not limited to the skin at the time of initial diagnosis (Stages IIB through IV). Median survival for late stage disease (Stages IIB, IIIA and IIIB) is reported to be 4.7, 4.7 and 3.4 years, respectively, and decreases further for Stage IV disease[3].

The etiology of MF is not known. MF commonly begins with a nonspecific scaly eruption that leads to the development of patches/plaques. With further progress, the disease advances with the formation of tumours, generalized erythroderma often with a leukemic phase (Sézary syndrome) and lymphadenopathy. Eventually, wide-spread visceral lymphoma may lead to death from the disease. Ulceration of tumours, with secondary infection with Staphylococcus aureus, Enterobacteriaceae and Pseudomonas aeruginosa, is also a common cause of morbidity and death. The diagnosis is made with skin biopsy and is further confirmed with immunophenotyping and DNA analysis of the T-cell receptor gene rearrangement to define the clonal population. Lymph node biopsies may be performed at initial staging in patients with overt advanced disease or if nodes are enlarged on physical examination or imaging studies. Peripheral blood is examined for the presence of circulating malignant cells which would serve to identify the leukemia expression of the Sézary syndrome.

Clinical staging serves to distinguish prognostic groups, where good-risk patients, who have plaque-only disease without lymph node, blood or visceral involvement have a better prognosis than intermediate-risk patients, with tumors, erythroderma or plaque disease with lymph node or blood involvement (with no visceral involvement), and poor-risk patients (with visceral involvement). Staging of patients with MF is essential not only for assessment of prognosis but also for decisions in management. The goals of treatment of patch/plaque disease without lymph node involvement (IA and IB), and those with enlarged but histologically uninvolved lymph nodes (IIA), is to achieve remission, relieve symptoms and achieve cosmetic improvement while avoiding long-term

[1] www.rarecare.eu

[2] Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002 Jan 1:97(1)72-81.

[3] Agar NS, Wedgeworth E, Crichton S, et al. 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;28:4730-9.

treatment-related toxicities. For patients with Stage IA, IB or IIA disease, management relies on the applications of skin directed therapies. The therapeutic options include topical corticosteroids, topical chemotherapy with chlormethine (also known as nitrogen mustard (NM) or mechlorethamine) or carmustine (BCNU), ultraviolet B (UVB) therapy, psoralen plus ultraviolet A radiation (PUVA) and total skin electron beam therapy. Targretin (bexarotene), an orally available capsule for systemic therapy, is indicated for advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients. Topical chlormethine is included in the EORTC (2006), the ESMO (2013) and NCCN (2014) guidelines as a first line therapy for early stage MF-type CTCL and for the treatment of cutaneous lesions in late stage MF-type CTCL.

About the product

Chlormethine is an alkylating agent that inhibits rapidly proliferating cells (ATC code L01AA05) and is used for the topical treatment of mycosis fungoides (MF)-type cutaneous T-cell lymphoma (MF-type CTCL). Chemically, the cytotoxicity of chlormethine is due to its spontaneous conversion to an electrophilic intermediate that covalently binds to cellular components. The highly reactive intermediate is an aziridinium ion formed by cyclisation of one of the side chains and displacement of a chloride ion[4,5,6,7,8]. Chlormethine has two reactive 2-chloroethyl side chains, classifying it as a bifunctional alkylating agent.

Alkylation of DNA is the primary basis for the cytotoxic actions of chlormethine. Chlormethine binds to N7 positions in guanines via its reactive chloroethyl moieties, potentially binding also to N3 positions in adenines[9, 10]. The bifunctional nature of chlormethine along with its small molecular size allows it to form interstrand cross-links within DNA, by alkylation of guanine-N7 positions in opposite DNA strands. Monoadducts and intrastrand biadducts are also formed, but the formation of interstrand cross-links makes chlormethine a more effective tumor chemotherapeutic agent than monofunctional analogues[11]. Unrepaired interstrand cross-links prevent transcription, replication, and segregation of DNA, and ultimately cause cell death[12]. There are numerous reports showing a correlation between the extent of DNA cross-linking and cytotoxicity[13] ; conversely, tumour resistance to bifunctional alkylating agents has been associated with increased capacity to repair DNA cross-links[14]. Defects in cell-cycle regulation that lead to cell-cycle progression before DNA damage can be repaired may also contribute to the sensitivity of cancer cells to these drugs[15,16]. Cell death caused by chlormethine may occur by multiple mechanisms leading to apoptosis or necrosis[17,18,19].

[4] Boyland E. The toxicity of alkyl-bis(beta-chloroethyl)amines and of the products of their reaction with water. Br J Pharmacol Chemother 1946;1:247-54.
[5] Gilman A, Philips FS. The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides. Science 1946;103:409-36.
[6] Anslow WP, Jr., Karnovsky DA, et al. The toxicity and pharmacological action of the nitrogen mustards and certain related compounds. J Pharmacol Exp Ther 1947;91:224-35.
[7] Hunt CC, Philips FS. The acute pharmacology of methyl-bis(2-chloroethyl) amine (HN2). J Pharmacol Exp Ther 1949;95:131-44.
[8] Wang QQ, Begum RA, Day VW, Bowman-James K. Sulfur, oxygen, and nitrogen mustards: stability and reactivity. Org Biomol Chem 2012;10:8786-93.
[9] Hemminki K, Kallama S. Reactions of nitrogen mustards with DNA. IARC Sci Publ 1986:55-70.
[10] Osborne MR, Wilman DE, Lawley PD. Alkylation of DNA by the nitrogen mustard bis(2-chloroethyl)methylamine. Chem Res Toxicol 1995;8:316- 20.
[11] Sunters A, Springer CJ, Bagshawe KD, et al. The cytotoxicity, DNA crosslinking ability and DNA sequence selectivity of the aniline mustards melphalan, chlorambucil and 4-[bis(2-chloroethyl)amino] benzoic acid. Biochem Pharmacol 1992;44:59-64.
[12] Dronkert ML, Kanaar R. Repair of DNA interstrand cross-links. Mutat Res 2001;486:217-47.
[13] Rink SM, Soloman MS, Taylor MJ, et al. Covalent structure of a nitrogen mustard-induced DNA interstrand cross-link: An N7-N7 linkage of deoxyguanosine residues at the duplex sequence 5'-d(GNC). J Am Chem Soc 1993;115:2551-7.
[14] McHugh PJ, Spanswick VJ, Hartley JA. Repair of DNA interstrand crosslinks: molecular mechanisms and clinical relevance. Lancet Oncol 2001;2:483-90.
[15] Hawkins DS, Demers GW, Galloway DA. Inactivation of p53 enhances sensitivity to multiple chemotherapeutic agents. Cancer Res 1996;56:892-8.
[16] Ben-Yehoyada M, Wang LC, Kozekov ID, et al. Checkpoint signaling from a single DNA interstrand crosslink. Mol Cell 2009;35:704-15.
[17] Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer 2011;11:467-80.

Type of Application and aspects on development

The application was submitted under Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Caryolysine, an aqueous formulation of chlormethine that was first authorised for the treatment of MF-type CTCL in France in 1949. Although Caryolysine still holds a valid license in France, it has not been marketed since 2006. Both Caryolysine and Ledaga contain the same active substance, the same strength, same route of administration and with the same proposed indication. However, the pharmaceutical form is different, whereas Caryolysine is a concentrate solution for dilution in water or sodium chloride, Ledaga is produced as a gel with other excipients. The applicant has claimed that bioequivalence cannot be demonstrated through bioavailability studies as the treatment is for topical use (EMA/CHMP/QWP/558185/2014) and no systemic exposure can be observed (see non-clinical discussion and clinical pharmacology discussion). The application is based on two studies, a multi-center, randomised, active controlled, non-inferiority clinical pivotal trial comparing Ledaga with chlormethine compounded in petroleum-based 0.02% chlormethine HCl ointment and an uncontrolled, multi-center, open-label extension of the pivotal study.

The Applicant has applied for the following indication:

"Chlormethine gel is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients."

The agreed indication is as follows:

Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients (see section 5.1).

Posology is proposed as follows:

A thin film of Ledaga should be applied once daily to affected areas of the skin.

Treatment with Ledaga should be stopped for any grade of skin ulceration or blistering, or moderately severe or severe dermatitis (e.g., marked skin redness with oedema). Upon improvement, treatment with Ledaga can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least 1 week, the frequency of application can be increased to every other day for at least 1 week and then to once-daily application if tolerated.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gel containing chlormethine hydrochloride equivalent to 160 µg / g of chlormethine as active substance.

Other ingredients are: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerol, lactic acid, hydroxypropylcellulose, sodium chloride, menthol racemic, disodium edetate, and butylhydroxytoluene.

The product is available in a white aluminium tube with an inner lacquer and an aluminium seal and a white polypropylene screw cap, as described in section 6.5 of the SmPC.

[18] Osawa T, Davies D, Hartley JA. Mechanism of cell death resulting from DNA interstrand cross-linking in mammalian cells. Cell Death Dis 2011;2:e187.
[19] Surova O, Zhivotovsky B. Various modes of cell death induced by DNA damage. Oncogene 2013;32:3789-97.

2.2.2. Active substance

General information

The chemical name of chlormethine hydrochloride is 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride or 2,2'-dichloro-N-methyldiethylamine hydrochloride or bis(2-chloroethyl)methylamine hydrochloride or N-methylbis(2-chloroethyl)amine hydrochloride corresponding to the molecular formula $C_5H_{11}Cl_2N{\cdot}HCl$ and has a relative molecular mass 192.51 g/mol. The structure is shown is Figure 1:

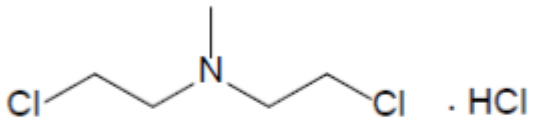


Figure 1: Structure of chlormethine hydrochloride

The structure of chlormethine hydrochloride was elucidated by using: chloride titration, elemental analysis, purity by gas chromatography, FT-IR spectroscopy, mass spectroscopy, ^{1}H NMR spectroscopy, DSC melting point, thermogravimetric analysis, and X-Ray powder diffraction.

Chlormethine hydrochloride is a white to off-white, crystalline hygroscopic solid compound, which is very slightly soluble in water, partially soluble in ethanol and soluble in acetone. The active substance does not exhibit stereoisomerism.

Polymorphism was determined by XRPD (X-ray Powder Diffraction analysis), data shown that although different crystallization principles and solvents were used, the same polymorph was obtained. Therefore, these data demonstrate that the same polymorphic form is constantly produced.

Manufacture, characterisation and process controls

The chlormethine hydrochloride manufacturing process consists of one chemical step starting from a commercially available starting material, N-methyldiethanolamine (MDEA). During evaluation, the CHMP requested to redefine MDEA as starting material, the applicant performed additional investigations in order to support the definition of MDEA as starting material following the principles of ICH guideline Q11. As a result of these investigations, the specifications for MDEA and chlormethine hydrochloride were significantly revised and in addition the distillation step of MDEA was defined and implemented as the first step of the synthesis of the active substance; these measures were considered satisfactory and MDEA was accepted as a starting material. However, although satisfactory, preliminary validation data have been presented sufficient to give some assurance that full validation is likely to be achievable, the validation data to support the proposed methods for control of impurities in MDEA has not been completed. Therefore, the CHMP recommends that the validation data should be completed before the marketing of the product.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in an amber glass jar, sealed with a PTFE-lined, threaded polypropylene screw-on cap which complies with the Ph Eur 3.2.1. and Regulation 2023/2006/EC.

Specification

The active substance specification includes tests for appearance, identification (IR, colorimetry), meting range (DSC), water content (Karl Fischer), pH, chloride (titration), assay (titration), related substances (GCs and ion chromatography), residual solvents (GCs), microbial limits (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set taking into account ICH S9 and M7 and considering that chlormethine hydrochloride active substance intended for advanced cancer indications and is itself genotoxic at therapeutic dose. The analytical methods used have been adequately described and non-compendia methods were appropriately validated in accordance with the ICH guidelines. except for titration (chloride content), GC (related substances), GC (resisual solvents), and ion chromatography (chloride content) Satisfactory preliminary validation data for this analytical methods of active substance and starting materials have been presented but the complete validation has not been completed. The CHMP recommended completing the validation data for these methods post authorisation. The CHMP also recommended to provide comparative batch analysis (for all parameters tested) by the active substance and finished product manufacturers. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested*:* assay, appearance, water content, pH and levels of individual and total impurities.

At both storage conditions (long term and accelerated) over the storage periods, all parameters complied with specification.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months at the recommended storage condition (25°C/60% RH) in the proposed container.

2.2.3. Finished medicinal product

The finished product is presented as a clear, free of particles, colourless gel, packaged in a re-sealable, aluminium tube, containing 60 g of gel for cutaneous use.

The goal of the pharmaceutical development was to provide a non-greasy, chemically stable, single phase cutaneous presentation in which the active substance is held in solution, and which dries rapidly upon application to the skin.

The active substance, chlormethine hydrochloride is known to be readily soluble in water and alcohols and therefore hydrophilic alcohol-based solvents were selected for the formulation in order to achieve a uniform

product. The physical characteristics of the active substance do not affect the formulation since the active substance is highly soluble in the solvents used in the finished product formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation used in the pivotal clinical trial is the same as the proposed commercial formulation.

A topical chlormethine hydrochloride formulation was developed using diethylene glycol monoethyl ether (DEGEE), glycerin, propylene glycol and isopropanol base. Compared to other topical formulations the developed formulation was considered improved on a number of characteristics and attributes appropriate for a topically administered anti-cancer product, including viscosity, drying time and lack of greasiness . Satisfactory studies have been performed to assure chlormethine hydrochloride remains solubilised in individual formulation components and final formulation base, during manufacture and over shelf-life. Data has been provided to assure that the active substance does not crystallise and that the formulation does not undergo phase separation under freeze-thaw conditions. Substantial data have been provided to demonstrate formulation understanding and provide assurance that the formulation is robust and fit for purpose.

The physical and chemical characteristics of the finished product formulation are that of a solution wherein approximately 97.7% (on a mass basis) of the materials are miscible with each other. The vast majority of the solids come from hydroxypropyl cellulose, which is the gelling agent. Optical microscopy was conducted on multiple batches. The samples were examined using a polarizing light microscope at up to 200 × magnification. There was no evidence of chlormethine hydrochloride visible particles observed in the samples. Furthermore, no evidence of multiple phases was observed. Sub-visible birefringent crystals and/or sub-visible particles observed in the samples were analysed by infrared spectroscopy and identified as formulation excipients (glycerol, edetate disodium and hydroxypropyl cellulose). Therefore, it was demonstrated that the active substance is fully soluble in the formulation and therefore the dosage form is considered a gel according to EDQM standard terms and Ph. Eur. monograph on semi-solid preparation for cutaneous application.

This non-sterile topical gel is largely alcoholic, containing a very limited amount of water (< 2.0%). No antimicrobial agents are incorporated as the finished product is acknowledged to be essentially self-preserving. The microbiological requirements of the Ph. Eur. (5.1.4) for preparations for cutaneous use are, therefore, applied. Tests for efficacy of antimicrobial preservation have been performed as part of development studies for clinical batches at 12-32 months following manufacture and on three batches of product, manufactured at the proposed commercial scale and facility at 5-7 months following manufacture. All results comply with Ph. Eur. requirements and demonstrate efficacy of antimicrobial preservation.

The finished product is packaged into aluminium foil tubes with a white exterior coating and lacquer interior coating. The dispensing end of the tube is sealed with an aluminium film and a white resealable screw-on cap. Product compatibility with the primary packaging components can be extrapolated from the finished release testing and stability testing results which show no indication of incompatibility. The lacquer complies with EU Directive 2002/72/EC as suitable for food contact. Given the potential hazards of this medicinal product, particularly to the eyes, coupled with its proposed use with domestic setting, a transparent sealable child-resistant plastic bag is provided. Each tube will be placed in the transparent plastic bag before being delivered to the patient. To support the claim of child resistance for the re-closable plastic bag, the CHMP recommended providing a certificate demonstrating compliance with BS EN ISO 8317 for re-closable packaging before the marketing of the product.

Manufacture of the product and process controls

The finished product is manufactured by producing sub-parts of the bulk gel and combining them followed by tube filling.

In-process controls of critical quality attributes (appearance, viscosity and homogeneity of chlormethine content assay) are described and are considered sufficient. Appropriate process validation has been performed in three batches at the proposed commercial scale. Process times and mixing speeds are reasonably consistent between batches. Results for in-process controls and ancillary test parameters are generally consistent within and between batches. For the bulk finished product, stratified sampling shows chlormethine assay values to be reproducible as are content of butyl hydroxytoluene and water content. Results for viscosity are similarly reproducible. The filling process is uniform, with fill weight reproducibility demonstrated across a range of filling speeds. However, the CHMP recommended performing quantitative cleaning validation during commercial-scale validation studies to support the proposed process to cleanse finished product residues from the exterior of the tube prior to labelling. Supplementary process validation data was presented for a further three batches which used the minimum, maximum and mid-point respectively of proposed mixing time and tube filling speed ranges. These data are consistent with those of the primary process validation batches. Satisfactory data were presented to support the proposed bulk hold times.

All in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, viscosity (Ph. Eur.), identity (HPLC/mass spectrometry), water content (Karl Fischer), identification of butylhydroxytoluene (HPLC), assay (HPLC/mass spectrometry), impurities (HPLC/mass spectrometry), tube uniformity (HPLC), minimum fill (gravimetry), uniformity of dosage unit by mass variation (Ph. Eur.) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented. The finished product will be released on the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on 3 commercial scale batches of finished product stored under long term conditions for 36 months at −25 to −15 °C and for up to 6 months under accelerated conditions at 2 to 8 °C according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, viscosity, water content, butylated hydroxytoluene content and assayThe analytical procedures used were the same as for release and are stability indicating.

At the recommended long-term storage condition, all data remain within the proposed specifications. These results showed that the product is stable when stored at the proposed long-term conditions.

Under accelerated storage conditions, no specific change nor trend is observed. However, an increase of several specified impurities and of the total impurities is observed. All data remain below the specification limit.

Studies were conducted to determine the effect of temperature on the finished product when cycled between refrigerated and room temperature conditions. Three batches of the finished product tubes are punctured, finished product content is dispensed from the tube, and then the tube is resealed with the tube cap closure. The tubes were exposed to conditions of 25 °C / 60% RH for 1 hour/day and then returned to refrigeration (2 to 8 °C) for up 16 weeks. No trend was observed. Stability-indicating impurities do show an increase over time, although all results remain within specification.

In order to confirm that the product behaves as predicted by all other stability data when the temperature transition occurs, additional studies have been conducted in which product has been stored at long-term conditions (−25 to −15 °C) for up to 18 months and then transferred to + 2 to + 8 °C for 6 months. The obtained stability data demonstrated that all results remain within the finished product specification.

A study of the finished product exposed to light under controlled light exposure per ICH Q1B method-defined conditions was conducted. These data support the conclusion that the primary packaging (tube) adequately protects the finished product from potential light exposure.

Based on available stability data, the proposed shelf-life of 36 months when stored in the freezer (-15°C to –25°C) and 60 days in the refrigerator (+2°C to +8°C) after defrosting as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. However a number of issues were recommended by the CHMP in relation to completion of analytical methods of the starting material and active substance, comparative batch analysis (for all parameters tested) by the active substance and finished product manufacturers, validation of cleaning of exterior of the tube and certification of compliance for the child-resistant re-closable bag. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Complete full analytical test method validation for:
    - MDEA GC method 1 (related substances)

- MDEA GC method 2 (ethylene oxide)
- GC (NM-OH in the drug substance)
- GC/MS (benzene, carbon tetrachloride and 1,2-dichloroethane in the drug substance)
- Ion chromatography (thionyl chloride in the drug substance)
- GC1 (individual and unspecified impurities in the drug substance)
- Chloride titration 1 (chloride content of the drug substance)

2. Provide comparative batch analysis (for all parameters tested) by the active substance and finished product manufacturers.

3. Perform validation of cleaning of exterior of tube prior to labelling as part of commercial-scale validation studies.

4. Provide certification of compliance to BS EN ISO 8317 for the child-resistant re-closable bag supplied with the finished product before the marketing of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant did not submit non-clinical studies. A summary of non-clinical characteristics of chlormethine were presented from the published literature and is described briefly in the following sections.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The cytotoxicity of chlormethine has been investigated in a number of human cell lines, and low IC_{50} values were shown for all. In the human colon adenocarcinoma cell line LS174T, the IC_{50} value was 0.27 µM using the sulphorhodamine B assay. The two human colon carcinoma cell lines Colo320DM and Colo320HSR, the human histiocytic lymphoma cell line U937, and the human leukemic T-cell lymphoblast cell line J6 had IC_{50} values of 1.0, 0.79, 4.1 and 0.55 µM, respectively, using a tetrazolium (MTT)-based colorimetric assay[20].

Secondary pharmacodynamic studies

Not available (see non-clinical discussion).

Safety pharmacology programme

Systemic administration of lethal or supra-lethal doses of chlormethine consistently produced adverse effects on the central nervous system in experimental animals. An i.v. injection of 20 mg/kg chlormethine to rabbits produced incoordination along with brief convulsive running movements, salivation, urination, defecation, lacrimation, bronchorrhea, and mioisis within 5 to 15 min of dosing. In mice, subcutaneous injection of 20 mg/kg and above produced tremors, depression, and intermittent convulsive activity followed later in survivors by incoordination, severe tremors, over-reaction to stimuli, coldness, diarrhoea, and retropulsive movements. Rats

[20] Smith KJ, Smith WJ, Hamilton T, et al. Histopathologic and immunohistochemical features in human skin after exposure to nitrogen and sulphur mustard. Am J Dermatopathol 1998;20:22-8.

surviving 3 to 4 days after an i.v. injection (dose not specified) exhibited increased irritability and abnormal movements, which was usually followed by death. Among survivors with less severe effects, hyperirritability persisting for weeks remained the only sign of injury. Extensive demyelination of the peripheral nerves was observed in a third of the rats[21].

In another study[22] , rats receiving a single i.v. dose of 0.16 mM/kg (approximately equivalent to 32 mg/kg) chlormethine HCl exhibited progressive muscular paralysis and terminal convulsive seizures prior to death within 2 to 4 h. i.v. doses of less than 0.02 mM/kg caused some delayed deaths. In cats, single i.v. doses of 0.04 and 0.08 mM/kg (approximately equivalent to 8 and 16 mg/kg) rapidly produced signs of licking, vomiting, salivation, and loose stools. From 20 to 30 min post-dosing, neurological changes starting with an inability to support the head were observed, followed by progressive paralysis with gross incoordination, asynergia, tremors, dilated pupils, profuse salivation, and complete prostration. Knee jerks were observed throughout paralysis, but without signs of muscular fasciculation or specific disturbance of placing or righting reflexes. Deaths occurred in less than 18 h. At 0.02 mM/kg, symptoms within 10 minutes of dosing included licking, vomiting, salivation, and loose stools. No paralysis was observed and convulsions were noted in only 1 of 3 cats at this dose. Deaths occurred between 1 to 3 days following progressive weight loss.

In the same study, a fall in blood pressure was observed in the cat following an i.v. dose of 0.01 mM/kg chlormethine[22] . Responses to vagal stimulation and to injected acetylcholine were not significantly altered by this dose. An i.v. dose of 0.02 mM/kg abolished the circulatory response to vagal stimulation but had no significant effect on responses to i.v. acetylcholine or epinephrine. Chlormethine was shown to stimulate the isolated rabbit and guinea pig duodenum, and these responses were prevented by adequate doses of atropine[22].

In dogs receiving a single i.v. dose of 1 mg/kg chlormethine (approximately the LD50), cardiovascular effects (decreased blood pressure, marked lack of oxygen saturation of the blood), reduction in body temperature, coldness of extremities, relaxation of anal sphincter, respiratory failure, body weight loss, terminal weakness and coma were observed prior to death usually between days 3 and 5 post-dosing. These effects arose secondary to the significant decrease in plasma and extracellular fluid volume, reduced total plasma proteins and chloride and reduction in red cells. These findings resulted at least in part from excessive emesis, which started within a few hours of dosing and increased in severity through the second and third days, and diarrhoea usually blood stained or frankly haemorrhagic, which occurred on the second to fourth day post-dosing. There was no evidence of renal vasoconstriction and renal blood flow increased in dogs at ≥24 h post-dosing; however, as circulatory failure occurred, renal blood flow decreased with no consistent change in the filtration fraction. No permanent neurological injury was observed in surviving dogs. Leucopenia was most marked on the fourth or fifth day postdosing. Gross pathology showed enteritis mainly in the small intestine along with effects on spleen and thymus, and histopathology also showed intestinal, lymphoid, and myeloid injury[23].

Pharmacodynamic drug interactions

The applicant did not submit studies or publications on pharmacodynamic drug interactions (see non-clinical discussion).

[21] Anslow WP, Jr., Karnovsky DA, et al. The toxicity and pharmacological action of the nitrogen mustards and certain related compounds. J Pharmacol Exp Ther 1947;91:224-35.
[22] Hunt CC, Philips FS. The acute pharmacology of methyl-bis(2-chloroethyl) amine (HN2). J Pharmacol Exp Ther 1949;95:131-44.
[23] Houck CR, Crawford B, et al. Studies on the mechanism of death in dogs after systemic intoxication by the intravenous injection of methyl-bis(Bchloroethyl) amine or tris(B-chloroethyl) amine. J Pharmacol Exp Ther 1947;90:277-92.

2.3.3. Pharmacokinetics

Absorption

Sensitive biomarker-based (mitotic index, protein, RNA and DNA synthesis) studies performed in mice using vaginal, rectal, and dermal administration indicate an absence of systemic or extended local exposure at doses/concentrations relevant to the therapeutic application of chlormethine gel.

In one study, female Swiss mice received a single intravaginal administration of a 1% solution of chlormethine in water and the incorporation of radiolabelled protein ([3H]leucine), RNA ([3H]uridine), and DNA ([3H]thymidine) precursors was measured as indicators of protein, RNA and DNA synthesis. Chlormethine completely inhibited DNA synthesis only in the vaginal cells (i.e., locally at the site of application), without evidence of systemic absorption (as measured by lack of effect on DNA synthesis in the rectum). Chlormethine did not affect RNA or protein synthesis in the vagina or rectum[24].

Inhibition of mitotic activity in the vaginal mucosa was reported in mice (n=9) receiving an intravaginal dose of 50 µl of 0.01% chlormethine (prepared in water); no evidence of systemic exposure was observed based on an assessment of mitotic activity in the rectal mucosa. Conversely, when mice (n=6) received a single intra-rectal dose of 0.01% chlormethine, mitosis in the rectal mucosa was blocked, but not in the vaginal mucosa, again showing no evidence of systemic exposure[25].

Another demonstration of local, but not systemic, anti-mitotic effects of chlormethine was reported in an animal model whereby ultraviolet (UV) light was used to induce epidermal hyperplasia in hairless HRS/J mice[26] . Chlormethine reduced the mitotic index and DNA synthesis only at the site of application (i.e., the neck) but had no effect on these parameters on a control area on the back, indicating that chlormethine effects were local and not systemic.

Distribution

Following i.v. administration, distribution of chlormethine-derived material other than to the local site has been reported. In mice, an i.v. dose of 35 mg/kg produced measurable levels of radioactivity in the brain, spinal cord, lungs, and submaxillary glands as determined by autoradiography, whereas in rats 16% of an administered dose (unspecified) was found in the spleen, lungs, kidneys, liver, and blood[27]; in dogs, a 3 mg/kg i.v. dose rapidly disappeared from the blood and produced low levels in tissues, with the highest levels in the bone marrow[28].

Metabolism

In water or body fluids, chlormethine undergoes rapid chemical transformation and combines with water or reactive compounds of cells, so that the drug is no longer present in active form. A significant loss of toxicity occurred upon incubation of chlormethine in blood ex vivo prior to its injection into rats[29] . The biological potency of chlormethine was shown to decrease rapidly as measured in mouse, cat, and rabbit arterial occlusion

[24] McCullough JL, Weinstein GD. Mouse vaginal assay for topically effective chemotherapeutic agents. J Invest Dermatol 1975;65:394-9.
[25] Van Scott, EJ, Bonder RH. Intravaginal and intrarectal screening of antimitotic drugs for topical effectiveness. J Invest Dermatol 1971;56: 132-139.
[26] du Vivier A, Stoughton RB. An animal model for screening topical and systemic drugs for potential use in the treatment of psoriasis. J Invest Dermatol 1975;65:235-7.
[27] IARC. Nitrogen mustard (hydrochloride). Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man 1975;9:193-207.
[28] Health Council of the Netherlands. Nitrogen Mustard (hydrochloride); Health-based occupational cancer risk values. The Hague. 2004.
[29] Skinner DB, Herbst AL, Raker JW. Factors influencing the metabolism of nitrogen mustard in blood and blood components. Correlation of colorimetric measurement with biologic toxicity. Bull Soc Int Chir 1964;23:63-74.

models[29, 30, 31,32]. Longer occlusion times resulted in protection from bone marrow damage; this followed a dose-response[31, 32].

After topical application, chlormethine may be transformed into three of the most common chlormethine degradation products that are formed in aqueous solutions: the half mustard N-methyl (β- chloroethyl) 2-hydroxyethylamine, the dimer N,N'-dimethyl-N,N' bis(2- chloroethyl)piperazinium, and N-methyldiethanolamine (MDEA)[4] . With the exception of the dimer, these transformations are likely to occur within minutes after contact with body constituents. The primary transformation product, the half mustard, is reactive[33] and will rapidly cyclize. It was shown to be at least as toxic as chlormethine in older toxicology studies[4,34]. These findings however, were not observed in the arterial occlusion and *ex vivo* incubation models described earlier in this section, in which degradation products produced significantly less mortality and toxicity. Neither the dimer nor MDEA showed antimitotic activity on mouse vaginal epithelium[33] . MDEA exhibits minimal acute toxicity (oral LD50 in rats of 4.78 g/kg and topical LD50 in rabbits of 6.24 g/kg)[35].

Excretion

Information was found on excretion of chlormethine following i.v. dosing at or above the LD50: in dogs administered 0.5–3 mg/kg, low levels of chlormethine were found in the urine; in rats, less than 20% of an administered dose of 3.3 mg/kg was recovered in the urine[28]; in mice, 15% of the dose (4 mg/kg) was eliminated as CO2, 5% in the urine, and 13% in the feces after 24 h[36].

2.3.4. Toxicology

Single dose toxicity

Single-dose studies have been performed in mice utilizing vaginal, rectal, or other local routes of application and concentrations ranging from 0.01–2% chlormethine (concentrations comparable to or up to 100-fold higher than those in the clinical studies in MF-type CTCL). Several studies investigated the acute toxicity of chlormethine after dermal application. In these studies the compound was applied at very high doses and was formulated in solvents that increase skin permeability (e.g., DMSO, chloroform).

Significant systemic toxicity, including mortality and local toxicity, were described after topical application of 700-fold the estimated highest daily dose used in the clinical study with chlormethine gel. Signs of systemic exposure to the parent drug were not observed in animals after topical application of aqueous formulations of chlormethine at concentrations up to 100-fold higher than the concentration in chlormethine gel. Margins to the human doses are shown in Table 1

[30] Lemire SW, Barr JR, Ashley DL, et al. Quantitation of biomarkers of exposure to nitrogen mustards in urine from rats dosed with nitrogen mustards and from an unexposed human population. J Anal Toxicol 2004;28:320-6.
[31] Mark VH, Miyazaki Y, Kjellberg RN, et al. Determination of the biologic Toxicity of circulating alkylating agents. Surg Gynec & Obst 1963;116:232-6.
[32] Ulfohn A, Kramer SP, Dorfman H, et al. The duration of the myelotoxic effects of circulating alkylating agents. Cancer Res 1964;24:1659-65.
[33] Van Scott EJ, Yu RJ. Antimitotic, antigenic, and structural relationships of nitrogen mustard and its homologues. J Invest Dermatol 1974;62:378-83.
[34] Fell HB, Allsopp CB. Tissue culture experiments on the biological action of methyl bis (beta-chlorethyl) amine and its hydrolysis products. Cancer Res 1949;9:238-46.
[35] Huntsman Corporation. Methyldiethanolamine (MDEA).
[36] Skipper HE, Bennett LL, Jr., Langham WH. Over-all tracer studies with C14 labeled nitrogen mustard in normal and leukemic mice. Cancer 1951;4:1025-7.

Table 1 Calculation of margins based on body weight for dermal application

		Mean clinical dose† 2.81 g gel / day	Highest clinical dose† 10.5 g gel / day
Animal data		**mg/kg* chlormethine** 0.0075	**mg/kg* chlormethine** 0.028
Study/Species	**Effect dose[mg/kg]**	**Margin**	**Margin**
Single dose studies in mice (Sharma)	20	2700	700
Single dose studies in mice (Tewari-Singh)	160	21,000	5700
Carcinogenicity in mice	15 (weekly) **	285	77
Carcinogenicity in mice	5 (weekly) **	95	26

*Assuming human body weight of 60 kg, 0.016% chlormethine per g gel. † In clinical study 201. **For margin calculation, daily human dose was multiplied by 7.

The topical LD50 values for chlormethine free base (≥99% pure) in two vehicles (PEG 300 and DMSO) were determined in female Swiss mice[37] . For chlormethine in PEG 300, the LD50 was 33.6 mg/kg (corresponding to a local concentration of 0.5 mg/cm^2). For chlormethine in DMSO, the LD50 was 20 mg/kg (corresponding to a local concentration of 0.3 mg/cm^2). Body weights were reduced from 24 h post exposure. Death occurred within 8 to 12 days following topical dosing. In the second phase of the study, chlormethine was administered topically at the LD50 dose in DMSO (*i.e.*, at 20 mg/kg). Body weight was significantly reduced when compared to controls at Days 3 (n=6) and 7 (n=4). In haematology, white blood cells (WBC) were decreased and red blood cells (RBC) were increased (Day 3). In clinical chemistry, alanine transaminase (ALT) and aspartate transaminase (AST) were increased (Days 3 and 7). At necropsy, decreased relative spleen weight and increased relative kidney weight were observed (Day 3). Furthermore, biochemical analysis of the liver revealed decreased hepatic glutathione (GSH) (Day 3) and oxidized glutathione (glutathione disulfide [GSSG]) (Days 3) and increased malondialdehyde (MDA; a measure of lipid peroxidation) (Days 3 and 7), and DNA fragmentation (Days 3 and 7).

In a second, similar study[38], chlormethine free base (≥99% pure) was administered in DMSO as a single topical dose at 0 or 20 mg/kg (corresponding to a local concentration on the skin of 0.68 mg/cm^2) to female Swiss mice (n=4 on Days 0–4, n=2 on Days 5 and 7, n=3 on Day 6). The following were observed as compared to the controls: body weights declined until Days 5-6; decreased WBC count from 24 h onwards with a maximum effect on Day 3 followed by subsequent increase; no change in RBC count or haemoglobin; decreased hepatic GSH within 24 h, reaching a maximum reduction on Day 7; increased glutathione dioxide at 24 h with progressive decreases below control levels on subsequent days; progressive increases in hepatic MDA (beginning on Day 2) and percent hepatic DNA damage (beginning on Day 1); no effect on liver and kidney weights; progressive decrease in spleen weight beginning on Day 1 until Day 4 with subsequent increase; no significant change in AST and ALT levels until Day 4, when the activities significantly increased; and no effect on alkaline phosphatase activity. In addition, in the same study, single topical doses of 5 or 10 mg/kg (n=5 or 6/group/time point, local concentrations on the skin were 0.17 mg/cm^2 and 0.34 mg/cm^2, respectively) were applied to female Swiss mice. Effects on WBC count, MDA, DNA damage, and spleen weight were observed, generally less pronounced when compared to 20 mg/kg, indicating a dose-response relationship.

[37] Sharma M, Vijayaraghavan R, Gautam A. DRDE-07 and its analogues as promising cytoprotectants to nitrogen mustard (HN-2)--an alkylating anticancer and chemical warfare agent. Toxicol Lett 2009;188:243-50.
[38] Sharma M, Vijayaraghavan R, Gautam A. DRDE-07 and its analogues as promising cytoprotectants to nitrogen mustard (HN-2)--an alkylating anticancer and chemical warfare agent. Toxicol Lett 2009;188:243-50.

In another study, female Swiss mice were treated with 20 mg/kg or DMSO as previously described[39,40] . Here, histopathology was performed on skin, liver, spleen, and kidney. Significant histopathological findings in liver included granulovascular degeneration with perinuclear clumping of the cytoplasm of hepatocytes. Hepatic lesions were characterised by congestion and haemorrhage. Kidneys showed minimal to severe proximal tubule atrophy, minimal to moderate haemorrhage, and necrosis of tubular parenchymal cells. Spleens showed vascular congestion and increases in hematopoietic precursor cells, along with hypocellularity of white pulp follicles. In the treated skin, there was focal keratinocyte swelling and epidermal necrosis in the stratum corneum, with swollen cells throughout the epidermis. Large amounts of inflammatory cells were observed in the dermal region. Histopathology changes were greater by Day 7 compared to Day 3 in liver, skin, and kidneys, but reduced or resolved by Day 7 in the spleen.

Tewari-Singh et al.[41] reported studies in which SKH-1 hairless and C57BL/6 (haired) mice (n=5) were exposed topically to 200 µL acetone alone or to 3.2 mg chlormethine hydrochloride in 200 µL acetone (corresponding to a dose of 160 mg/kg) for 12 h, 24 h, 72 h and 120 h. Untreated controls were included in the study. Following the above mentioned exposures, mice were euthanised, and the dorsal skin was collected and investigated. Chlormethine hydrochloride treatment caused edema, erythema, microblister formation, pigmentation changes, dry skin, and wounding on the skin of SKH-1 hairless and C57BL/6 mice. Histopathologically, effects consisted of increased epidermal thickness, epidermal-dermal separation, necrotic/dead epidermis, epidermal denuding, scab formation, parakeratosis, hyperkeratosis, and acanthosis with hyperplasia[42].

Repeat dose toxicity

No repeat dose toxicity studies or publications were submitted (see non-clinical discussion).

Genotoxicity

Fox and Scott[43] and Povirk and Shuker[44] have published comprehensive reviews of the mutagenicity of chlormethine. Reversions were reported in several bacterial and fungal strains, mutations were reported in plant strains, dominant and recessive lethal mutations occurred in insect strains, and dominant lethal and forward mutations occurred in mammalian strains. In addition, cytogenetic effects (structural and numerical aberrations) have been reported in plant, human, and rodent cells. These data confirm that chlormethine is mutagenic in bacterial, plant, and mammalian cells.

Chlormethine was positive in the Ames assay[45] . Metabolic activation was not required to produce mutagenicity. A dose-related increase in revertant colonies was observed at all concentrations tested (10 to 40 µg/plate). Similar findings were reported by Bruce and Heddle[46] .

[39] Sharma M, Pant SC, Pant JC, Vijayaraghavan R. Nitrogen and sulphur mustard induced histopathological observations in mouse visceral organs. J Environ Biol 2010;31:891-905.
[40] Sharma M, Vijayaraghavan R, Agrawal OP. Comparative toxic effect of nitrogen mustards (HN-1, HN-2, and HN-3) and sulfur mustard on haematological and biochemical variables and their protection by DRDE-07 and its analogues. Int J Toxicol 2010;29:391-401.
[41] Tewari-Singh N, Jain AK, Inturi S, et al. Clinically-relevant cutaneous lesions by nitrogen mustard: useful biomarkers of vesicants skin injury in SKH-1 hairless and C57BL/6 mice. PLoS One 2013;8:e67557.
[42] Tewari-Singh N, Jain AK, Orlicky DJ, et al. Cutaneous injury related structural changes and their progression following topical nitrogen mustard exposure in hairless and haired mice. PLoS One 2014;9:e85402.
[43] The genetic toxicology of nitrogen and sulphur mustard. Mutat Res 1980;75:131-68.
[44] Povirk LF, Shuker DE. DNA damage and mutagenesis induced by nitrogen mustards. Mutat Res 1994;318:205-26.
[45] Benedict WF, Baker MS, Haroun L, et al. Mutagenicity of cancer chemotherapeutic agents in the Salmonella/microsome test. Cancer Res 1977;37:2209-13.
[46] The mutagenic activity of 61 agents as determined by the micronucleus, Salmonella, and sperm abnormality assays. Can J Genet Cytol 1979;21:319-34.

Chlormethine has been reported to induce chromosome aberrations[47,48], DNA damage *in vitro*[49,50] , and mutations in peripheral human lymphocytes exposed to chlormethine *in vitro*. The IC50 for induction of hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus mutations in the T lymphocytes was 1.34 µM for a 30 min exposure period. The IC50 for growth inhibition was in the range of 0.5-3.7 µM for the individual lymphocyte populations from nine different donors[50].

In *Drosophila* flies, chlormethine (0.5 and 1 mM), administered via an abdominal injection, produced an increase in recessive lethal mutations; mutagenic activity observed was mainly a result of the formation of DNA crosslinks whereas DNA monoadducts were responsible for only a minor contribution to the mutagenic activity[51].

Mutagenicity

Male Dub:(ICR) mice were treated i.v. with chlormethine at doses ranging from 0.1 to 3.75 mg/kg and were mated to untreated females 7 to 20 days post-treatment to assess the occurrence of dominant lethal mutations[52]. A dose-related increase in mutations was observed in the embryos. Similar findings were reported when male Dub:(ICR) mice were given a single i.v. injection of 2 mg/kg and 5 weeks later were mated to untreated females[53]. The matings continued for 5 weeks. Chlormethine produced a statistically significant increase in dominant lethal mutations in the embryos.

Carcinogenicity

Zackheim and Smuckler[54] investigated the carcinogenic effect of chlormethine after topical application to mice. Female Swiss mice were exposed topically (to the shaved mid-back) to doses of 0.1 and 0.3 mg chlormethine in 95% ethanol (approx. 5 and 15 mg/kg, respectively) for 20 to 33 weeks. When mice were exposed to 0.3 mg chlormethine once per week, 8 of 24 animals developed skin tumours (7 animals with papillomas and 1 squamous cell carcinoma) after 20 weeks of treatment. Administration of 0.1 mg chlormethine once per week produced no tumours in 30 animals after 33 weeks. Administration of 0.1 mg of chlormethine three times per week produced skin papillomas with no squamous cell carcinoma in 6/29 animals after 26 weeks of treatment. No skin tumours developed in the 34 controls. Irritant dermatitis, alopecia, and scarring were observed in a high percentage of the chlormethine-treated animals at 0.1 mg three times weekly and 0.3 mg weekly.

Epstein[55] investigated the effect of chlormethine on UVB irradiation-mediated tumour formation in hairless mouse skin. 0.1 mg chlormethine per animal in 95% ethanol (approx. 5 mg/kg) or vehicle were applied weekly for 52 weeks to the posterior halves of the backs of four groups of Ucsd (Hr) albino hairless mice (n=42 to 54/group) without and with UVB irradiation (1.98 x 102 mJ/cm^2, 3 times per week). Treatment with chlormethine/UVB resulted in faster cutaneous tumour formation than ethanol/UVB. The first skin tumours were

[47] Biesele JJ, Philips FS, Thiersch JB, et al. Chromosome alteration and tumour inhibition by nitrogen mustards; the hypothesis of crosslinking alkylation. Nature 1950;166:1112-4
[48] Evans HJ, Scott D. The induction of chromosome aberrations by nitrogen mustard and its dependence on DNA synthesis. Proc R Soc Lond B Biol Sci 1969;173:491-512.
[49] Masta A, Gray PJ, Phillips DR. Molecular basis of nitrogen mustard effects on transcription processes: role of depurination. Nucleic Acids Res 1994;22:3880- 6.
[50] Olsen LS, Korsholm B, Nexo BA, Wassermann K. Nitrogen mustard mediated mutagenesis in human T-lymphocytes in vitro. Arch Toxicol 1997;71:198-201.
[51] Wijen JP, Nivard MJ, Vogel EW. The in vivo genetic activity profile of the monofunctional nitrogen mustard 2-chloroethylamine differs drastically from its bifunctional counterpart mechlorethamine. Carcinogenesis 2000;21:1859-67.
[52] Goldstein LS. Use of an in vitro technique to detect mutations induced by antineoplastic drugs in mouse germ cells. Cancer Treat Rep 1984;68:855-8
[53] Goldstein LS. Dominant lethal mutations induced in mouse spermatogonia by mechlorethamine, procarbazine and vincristine administered in 2-drug and 3-drug combinations. Mutat Res 1987;191:171-6.
[54] Zackheim HS, Smuckler EA. Tumorigenic effect of topical mechlorethamine, BCNU and CCNU in mice. Experientia 1980;36:1211-2.
[55] Epstein JH. Effects of mechlorethamine (HN2, nitrogen mustard) on UV-induced carcinogenesis in hairless mouse skin. J Natl Cancer Inst 1984;72:383- 5.

observed after 21 weeks in the chlormethine/UVB group and after 28 weeks in the ethanol/UVB group. Furthermore, administration of chlormethine/UVB increased the tumour size as compared to ethanol/UVB. Tumours reached 50 mm^3 by 22 weeks and 100 mm^3 by 24 weeks in the chlormethine/UVB group. Tumours reached 50 mm^3 and 100 mm^3 by 32 weeks in the ethanol/UVB group. Neither chlormethine alone nor ethanol alone without UVB irradiation produced skin tumours. The skin of the animals in these groups without UVB irradiation showed no gross evidence of damage, thickening, desquamation or premalignant changes at the termination of the study.

In a second, similar study by Epstein[56] , a higher dose of chlormethine was used compared to the study described above. A dose of 0.1 mg chlormethine per animal applied twice weekly without UVB produced skin tumours in 34% of the mice. The chlormethine treatments plus UVB radiation resulted in a significant acceleration of tumour formation as compared to either carcinogenic stimulus alone. The twice-weekly application of chlormethine in presence of UVB exposure was more tumorigenic than once-weekly application of chlormethine in presence of UVB.

Reproduction toxicity

Fertility and early embryonic development

Chlormethine, administered to male Wistar rats via i.v. injection at doses of 0.1, 0.25, and 0.5 mg/kg every 2 weeks for 24 weeks (i.e., 12 doses), produced significantly impaired fertility at 0.25 and 0.5 mg/kg[57]. The effect was generally not reversible after 40 weeks of recovery. No fertility effects were noted at 0.1 mg/kg. Mortality was observed at 0.5 mg/kg, where 31% of the treated males died. There was no significant effect on numbers of foetal implants at any dose level.

When chlormethine was administered as a single i.p. or i.v. injection at doses ranging from 0.02 to 4 mg/kg to male mice, 3 mg/kg was cytotoxic to spermatogonia and spermatocytes as assessed on Day 11. A dose-related decrease in sperm head count occurred at doses of 1 mg/kg and higher on Day 29; this effect was not observed at Day 56[58] .

Chlormethine was administered i.p. to male and female C57 BL/6J mice for 4 consecutive days at a dose of 0.5 mg/kg. Two weeks later, treated males were mated with treated females. The pregnancy rate was 80% for untreated males paired with untreated females and 12.5% for treated males paired with treated females. In the treated groups, mean litter size was reduced and none of the offspring survived[59].

Embryo-fœtal development

Female mice (n=78) received a single i.p. injection of 1 to 2 mg/kg on Gestation Day (GD) 10, 11, or 12 and the fetuses were examined on GD 14 or later[60]. Many of the fetuses died, but 178/475 exhibited malformations, with 150 of the foetuses exhibiting malformations in the foot. A single s.c. injection of 2.5 mg/kg on GD 6 to 13 to female mice produced malformations primarily involving defects of the extremities (i.e., limbs and digits); embryo lethality was also observed mainly on GD 8 to 10[61].

[56] Epstein JH. Nitrogen mustard (mechlorethamine) and UVB photocarcinogenesis: a dose response effect. J Invest Dermatol 1984;83:320-2.
[57] Cooke RA, Nikles A, Roeser HP. A comparison of the antifertility effects of alkylating agents and vinca alkaloids in male rats. Br J Pharmacol 1978;63:677- 81.
[58] Meistrich ML, Finch M, da Cunha MF, et al. Damaging effects of fourteen chemotherapeutic drugs on mouse testis cells. Cancer Res 1982;42:122-31.
[59] Chryssanthou CP, Wallach RC, Atchison M. Meiotic chromosomal changes and sterility produced by nitrogen mustard and procarbazine in mice. Fertil Steril 1983;39:97-102.
[60] Danforth CH, Center E. Nitrogen mustard as a teratogenic agent in the mouse. Proc Soc Exp Biol Med 1954;86:705-7.
[61] Nishimura H, Takagaki S. Congenital malformations in mice induced by nitrogen mustard. Acta Sch Med Univ Kioto 1959;36:20-6.

Pregnant female Swiss mice (n=4/group/timepoint) received a single i.p. injection of chlormethine (0.1 to 1 mg/kg) on GD 11 or 12 and the embryos were harvested on GD 12[62]. The embryo was dispersed into a cell suspension and evaluated for chromosomal aberrations. Following a 6-hour exposure, the frequency of metaphases with chromosomal aberrations was 1.3% (untreated control), 1.2% (saline control), and 6.9, 48.7, and 82.5% (chlormethine at 0.1, 0.5 and 1 mg/kg, respectively). In addition, doses of 0.5 and 1 mg/kg increased the number of multiple aberrations and pulverized chromosomes. Similar effects were observed following a 2-hour exposure to 1 mg/kg and continued to be evident at times up to a 24-h exposure. Finally, when 5 females were dosed on GD 11 at 1 mg/kg and sacrificed on GD 19, 47 viable foetuses with a mean body weight of 0.9 grams were obtained with 15 resorptions and 2 late deaths. In the 5 female controls, there were 60 viable foetuses with a mean body weight of 1.27 grams, with 1 early and 2 late deaths. Approximately 40% of the chlormethine-treated foetuses exhibited gross malformations, primarily in the limbs. No malformations occurred in the controls.

Female rats received single s.c. injections of 1 mg/kg on GD 12, 13, 14, or 15 and the foetuses were removed on GD 21. Foetal mortality or resorptions were observed after treatment on GD 12 or GD 13 and abnormal foetuses were observed after treatment on GD 13 and 14. When the dose was split in 2 x 0.5 mg/kg over 2 days, no abnormalities were observed on GD 15[63]. A single s.c. injection of 1 mg/kg to pregnant rats on GD 12 or 13 produced external malformations in 90% of the foetuses, including primarily general growth retardation, small meningocele, short mandible, syndactyly, and short kinky tail[64]. When the same treatment regimen was followed and the embryos were examined for chromosomal aberrations, the percentage of abnormal metaphases was 0.8% at 6 h, approximately 14% to 18% at 12 to 18 h, and approximately 3% at 24 h as compared to 0.1% in the controls.

Pre-and postnatal development

The applicant did not submit data on pre- and postnatal development studies (see non-clinical discussion).

Toxicokinetic data

The applicant did not submit data or publications on toxicokinetic (see non-clinical discussion).

Local tolerance

Ocular administration of 1% chlormethine to the rabbit eye resulted in an irritation response characterised by conjunctival and iridial hyperemia, ocular hypertension, increased protein in the aqueous humour, and miosis[65].

Other toxicity studies

Excipient safety evaluation

Topically applied, DEGEE has LD50 values of 6000 mg/kg for rats and mice and 4200-8300 mg/kg for rabbits without producing dermal toxicity[66].

[62] Meyne J, Legator MS. Clastogenic effects of transplacental exposure of mouse embryos to nitrogen mustard or cyclophosphamide. Teratog Carcinog Mutagen 1983;3:281-7.
[63] Haskin D. Some effects of nitrogen mustard on the development of external body form in the fetal rat. Anat Rec 1948;102:493-511.
[64] Soukup S, Takacs E, Warkany J. Chromosome changes in embryos treated with various teratogens. J Embryol Exp Morphol 1967;18:215-26.
[65] Jampol LM, Axelrod A, Tessler H. Pathways of the eye's response to topical nitrogen mustard. Invest Ophthalmol 1976;15:486-9.
[66] Opinion on diethylene glycol monoethyl ether. Scientific Committee on Consumer Safety; 26 February 2013, revision of 18 June 2013.

DEGEE administration was well tolerated after repeated dosing. Dermal administration of 100% purified DEGEE up to a high dose of 1000 mg/kg/day in NZW rabbits or 40% DEGEE in water in NZW rabbits or rats did not lead to significant systemic toxicity.

DEGEE was neither teratogenic nor embryotoxic in Sprague-Dawley rats dosed topically four times per day (at 2.5 hour intervals) on GD 7 to 16 with 0.35 mL/application. Maternal weight gain was lower than in the controls (treated with water) which provided evidence of systemic exposure[67].

There was no evidence of *in vitro* or *in vivo* genotoxicity with DEGEE[66].

DEGEE was not carcinogenic in a GLP-compliant, 26-week topical carcinogenicity study in Tg.AC mice, in which DEGEE was used as the vehicle[68]. As detailed in a review publication[69], there is no evidence for carcinogenicity of DEGEE based on use of 40% DEGEE in aqueous solution as an oral dose control arm in a rat study over 92 weeks for females and 100 weeks for males. In a 52-week albino hairless mouse study in which animals were treated with a cumulative UV dose (600 Robertson-Berger units/week), the 5% dapsone topical gel vehicle containing 25% DEGEE did not cause an increased incidence of tumours or reduce time to tumor development[69].

DEGEE Exposure and safety margin assessment

The mean daily clinical dose (DD) of chlormethine gel in the clinical trials was 2.81 g; the estimated highest daily dose of chlormethine gel in a single subject was 10.5 grams. DEGEE is present in the Gel at 49.91%. A dermal absorption of 50.4% of an applied DEGEE dose can be assumed, resulting in a mean clinically absorbed dose of 11.8 mg/kg/day and a maximal clinically absorbed dose of 44 mg/kg/day.

Topical administration of diethylene glycol monoethyl ether (DEGEE) to rabbits resulted in a NOAEL of 1000 mg/kg/day in a 28-day study. When comparing the NOAEL with the estimated highest daily clinical dose of DEGEE with chlormethine gel, the safety margin is 22.7 based on body weight. For the mean daily clinical dose of 2.81 g chlormethine gel, the safety margin is 85 based on body weight.

Oral administration of DEGEE to dogs also resulted in a NOAEL of 1000 mg/kg/day in a 90-day GLP study. The resulting safety margins for the estimated highest daily dose of chlormethine gel are 22.7 based on weight and 12.6 based on human equivalent dose (HED). For the mean DD, the safety margin is 85 based on weight and 46 based on HED.

2.3.5. Ecotoxicity / environmental risk assessment

An environmental risk assessment report was provided for evaluation of chlormethine gel. A Phase I estimation of exposure has been performed for chlormethine hydrochloride, since the use of chlormethine gel increases environmental exposure to chlormethine hydrochloride.

Screening for persistence, bioaccumulation and toxicity

According to the CHMP guideline on the *Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00, 1 June 2006), drug substances with a log Kow > 4.5 should be screened for persistence, bioaccumulation and toxicity. The measurement of the log Kow of chlormethine hydrochloride

[67] Hardin BD, Goad PT, Burg JR. Developmental toxicity of four glycol ethers applied cutaneously to rats. Environ Health Perspect 1984;57:69-74.
[68] Chanda S, Erexson G, Frost D, et al. 26-Week dermal oncogenicity study evaluating pure trans-capsaicin in Tg.AC hemizygous mice (FBV/N). Int J Toxicol 2007;26:123-33.
[69] Osborne DW. Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products. J Cosmet Dermatol 2011;10:324-9

should be assessed with an aqueous buffer set at a chosen pH so that mainly the neutral form of the molecule is present ("Shake-Flask method", OECD 107).

As chlormethine hydrochloride is an ionisable molecule due to a basic function with a pKa of 6.4 (TOXNET 2014), the neutral form of the molecule is predominant in aqueous solution at pH much above 6.4.

Therefore the measurement must be performed at pH = 7.4 or optimally at pH = 8.4 where 99% of the molecule is neutral. However, a dedicated stability study of chlormethine hydrochloride in aqueous buffered solutions at pH = 7.4 and pH = 8.4 showed its rapid decomposition (YAU-R5624): at the time-point 0 minute, chlormethine hydrochloride degraded ~50% at both pH values. By 30 minutes, 1 hour and 2 hours, degradation at both pH values was ~90%, 98–99% and 100%, respectively. Therefore, the log Kow of chlormethine hydrochloride could not be determined experimentally, and only the estimated log Kow value of −1.24, was used.

An Fpen default value of 0.01 (1%) is proposed in the guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 1 June 2006). However, if data (reasonably justified market penetration data, e.g., based on published epidemiological data) are available to estimate a more accurate refined Fpen, this may be used. According to recent epidemiological data the number of people affected with MF-type CTCL in the EU-28 population is estimated to be 11,735, using available information[2]. This would correspond to an overall prevalence of MF-type CTCL in the EU of 0.22 per 10,000. This is the basis for estimating refined Fpen.

The worst-case (highest) calculation of the PECSURFACEWATER is shown below.

$$\text{PECSURFACEWATER of chlormethine HCl} = \frac{\text{DOSEai} \times \text{Refined Fpen}}{\text{WASTEWinhab} \times \text{DILUTION}}$$

$$\text{PECSURFACEWATER (mg/L)} = \frac{2.1 \times 0.000022}{200 \times 10}$$

PECSURFACEWATER of chlormethine HCl = 0.000023 µg/L

In the worst-case predicted surface water concentration for chlormethine hydrochloride is 435 times lower than this default threshold value (action limit).

2.3.6. Discussion on non-clinical aspects

Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells. Chlormethine gel, a topical formulation of 0.016% w/w chlormethine (0.02% w/w as chlormethine hydrochloride), has been developed for the treatment in adult patients of mycosis fungoides type cutaneous T-cell lymphoma (MF-type CTCL). The applicant submitted non-clinical literature to support the application which was considered to be acceptable in view of the known pharmaco-toxicological properties and the extensive clinical experience with chlormethine.

The available literature shows effects of toxic systemic doses of chlormethine on the function of vital organ systems. The relevance of these data (generated in the period 1947-1949) is considered to be limited as the investigated dose levels were often beyond the maximum tolerated dose. Biomarker-based studies performed in mice using vaginal, rectal, and topical administration indicated an absence of systemic or extended local exposure at doses/concentrations relevant to the therapeutic application of chlormethine gel. These published nonclinical studies support a lack of any significant systemic exposure to chlormethine following topical application of chlormethine gel. Thus the lack of secondary pharmacology programme is considered acceptable. This conclusion is in line with ICH S7A (Safety Pharmacology Studies for Human Pharmaceuticals), which states in Section 2.9 that safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low.

It appears that the metabolism of chlormethine is not fully known. It is possible that after topical application chlormethine is transformed into three of the most common chlormethine degradation products that are formed in aqueous solutions: the half mustard [N-methyl ß-chloroethyl) 2-hydroxyethylamine], the dimer N,N'-dimethyl-N,N' bis(2-chloroethyl)piperazinium, and N-methyldiethanolamine (MDEA). With the exception of the dimer, these transformations are likely to occur within minutes after contact with body constituents although the rate of transformation in skin is unknown. As no signs of systemic exposure to chlormethine were observed in animals after topical application, no excretion of the test compound or its degradation products is expected. There are no anticipated systemic interactions involving chlormethine or its metabolites following topical administration of chlormethine gel, given the lack of detectable systemic exposure.

The single dose toxicity of chlormethine has been adequately characterised in the published literature. Topical application of 0.01% – 2% chlormethine to animals, concentrations comparable to or up to 100-fold higher than in chlormethine gel, did not lead to systemic toxicity, suggesting absence of relevant systemic exposure to chlormethine.

Chlormethine was genotoxic both *in vitro* and *in vivo*. The genotoxicity of chlormethine is well established, since its pharmacological mechanism of action is primarily due to DNA cross-linking. Chlormethine was shown to be genotoxic in bacterial, plant, and mammalian cells. Chlormethine was carcinogenic in rat and mouse carcinogenicity studies after subcutaneous and intravenous administration.

Chlormethine was carcinogenic following dermal, i.v., s.c., and i.p. administration in mice and/or rats. Dermal application of chlormethine to mice at a dose of 15 mg/kg for up to 33 weeks resulted in skin tumours (squamous cell carcinomas and skin papilloma). There were no reports of systemic tumours after topical administration of chlormethine., which is consistent with no relevant systemic availability of chlormethine.

Chlormethine adversely affected male fertility and was embryotoxic and teratogenic in mice and rats after systemic chlormethine administration. Intravenously administered chlormethine impaired male fertility in rats at a daily dose of ≥ 0.25 mg/kg for 2 weeks. No dedicated animal studies on the effects of chlormethine on female fertility have been reported in the literature. Chlormethine caused foetal malformations in mice and rats when given as single injections of 1–2.5 mg/kg. Other findings in animals included embryo-lethality and growth retardation when administered as a single injection. Chlormethine is not recommended during pregnancy and in women of child bearing potential not using contraception.

There was no information on pharmacodynamic drug interaction, repeated-dose toxicity, toxicokinetic data, and in pre-and postnatal development presented. The systemic and local toxicities are well characterised and thus, the lack of studies is acceptable and no further non-clinical studies are considered necessary.

The toxicity of DEGEE following topical administration was well characterized. DEGEE is neither genotoxic, carcinogenic nor teratogenic.

The absence of systemic exposure after dermal application of chlormethine at relevant concentrations limits potential toxicity to local effects. Topical administration appeared to be well tolerated up to high doses. However, nitrogen mustards are vesicants causing skin, eye, and respiratory tract injury. Thus, dermal irritation and hypersensitivity reactions are expected (see clinical safety). No additional local toxicity studies for the gel formulation are considered necessary.

Chlormethine hydrochloride is not a PBT substance as log Kow is much below 4.5 and hence, an assessment of chlormethine hydrochloride for persistence, bioaccumulation and toxicity was not considered necessary. The Phase I action limit of 0.01 µg/L is not exceeded for chlormethine hydrochloride from the use of chlormethine gel. In the worst-case, predicted surface water concentration for chlormethine hydrochloride is 435 times lower

than this default threshold value (action limit). It is expected that the relative half-life of the active form of the compound is short in water and body fluids, chlormethine undergoes rapid chemical transformation and combines with water or reactive compounds in cells. Thus, chlormethine gel does not appear to represent a risk to the environment. However, chlormethine hydrochloride should be used according to the precautions stated in the SmPC section 6.6 (any unused medicinal product or waste material, including nitrile gloves used for application, must be disposed of in accordance with local requirements) in order to minimise any potential risks to the environment.

Non-clinical information has been reflected in section 5.3 and relevant statements have been included in SmPC section 4.6.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical effects of chlormetine containing products have been well established in a comprehensive literature review. There is extensive and long term clinical experience with the test substance and no additional nonclinical studies are considered.

Ledaga is not expected to pose a significant risk to the environment.

Information has been adequately reflected in the SmPC sections 4.6, 5.3 and 6.6.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a gel containing chlormethine. The applicant conducted a non-inferiority study comparing the test product with a petroleum-based 0.02% chlormethine HCl ointment (Aquaphor® ointment, AP). No bioequivalence study was conducted.

No scientific advice by the CHMP was requested for this medicinal product.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

Table 2: Tabular overview of clinical studies

Study 201 Study objectives	Patients	Treatment	Study design
To evaluate efficacy and safety of 0.02% chlormethine gel in patients with Stage I or IIA biopsy confirmed MF Post-treatment safety follow-up	260 (130 with chlormethine gel and 130 with AP) 255 patients received at least one	Once daily topical treatment for up to 12 months. Investigational drug: Chlormethine gel 0.02%	Multi-centre, Randomized, active-controlled, non-inferiority, single-blinded

for an additional 12 months.	dose of study medication	Comparator drug: Chlormethine 0.02% in an Aquaphor ointment (AP)	(observer)
Study 202 Study objectives	**Patients**	**Treatment**	**Study design**
Safety and efficacy of 0.04% chlormethine gel in patients who completed 12 months' treatment with chlormethine in study 201, without a complete response	98	Once daily topical treatment for up to 30 weeks Chlormethine gel 0.04%	Single-arm, open-label, extension study

2.4.2. Pharmacokinetics

Absorption

Study 201 (pivotal study)

Study 201 was a multi-centre, randomised study comparing the efficacy, tolerability and safety of 0.02% chlormethine gel with AP in patients with MF. In a cohort of patients, blood samples were collected pre-dose at the baseline visit and 1, 3 and 6 hours after the first application of study treatment and at pre-dose the month 1 visit (see methods section in 2.4.6.). Samples were analysed using HPLC method

Results

Plasma samples were collected from 23 patients (16 patients treated with chlormethine gel and 7 patients treated with AP, including patients who received whole body treatment. No measurable plasma concentrations of chlormethine were observed in any of the samples assayed.

Study 202 (extension study)

Study 202 was an open-label, single-arm study in patients who had completed study 201 but who had not achieved a complete response. Patients received up to 7 months of further treatment with a higher strength of chlormethine gel, 0.04%. Plasma samples were collected prior to treatment and 1 h after treatment at the baseline visit (or month 2 or 4 if the patient had already started the trial). A third sample per patient was also scheduled for collection prior to treatment and 1 h after application after 4 or 6 months' exposure. Samples were analysed using LC/MS/MS method (see methods section in 2.4.6).

Results

Plasma samples were collected from 15 patients. For all 39 plasma samples assayed, the concentrations of chlormethine and half-mustard were below the LLOQ. Further, the chromatograms were examined, and there were no detectable peaks, based on lower limits of detection estimated to be 0.3 ng/mL for chlormethine and 1.0 ng/mL for half-mustard.

2.4.3. Pharmacodynamics

The applicant did not submit pharmacodynamic studies (see pharmacology discussion).

2.4.4. Discussion on the pharmacology aspects

In clinical study 201 there was no evidence of systemic exposure following topical application of chlormethine gel. In study 202 there was also no evidence of systemic exposure following topical application of the higher strength gel, thus confirming the lack of systemic exposure at the recommended topical doses of chlormethine gel that has been seen in non-clinical studies. Patients who received chlormethine gel in Study 201 had no measurable concentrations of chlormethine in blood collected 1, 3 and 6 hours post-application on Day 1, and at the first month visit. Similarly, patients who received chlormethine gel 0.04% in a follow-up study (Study 202) had no measurable concentrations of chlormethine or its degradation product (half-mustard) in blood collected 1 hour post-application on Day 1 or after 2, 4, or 6 months of treatment (See SmPC section 5.2.). Animal safety pharmacology data collected from publications (see discussion on non-clinical aspects) are considered supportive of the pharmacological effect of chlormethine in humans. In view of these findings and since there is extensive clinical safety experience with chlormethine gel and related formulations, no further pharmacological studies are required.

2.4.5. Conclusion on the pharmacology aspects

The clinical pharmacology of chlormethine gel is considered to have been adequately evaluated from the data in the Studies 201 and 202. There was no evidence of systemic exposure following topical application of chlormethine gel. There was also no evidence of systemic exposure following topical application of the higher strength gel. It has been demonstrated that there is no systemic exposure to chlormethine following local cutaneous administration of chlormethine gel. Therefore, the lack of dedicated PK and PD studies are acceptable.

2.4.6. Clinical efficacy

Study 2005NMMF-201-US: Phase II pivotal trial to evaluate the safety and efficacy of nitrogen mustard (NM) 0.02% ointment formulations in patients with stage I or IIA mycosis fungoides (MF)

Methods

Main inclusion criteria

- A diagnosis of stage I or IIA (cutaneous only) mycosis fungoides confirmed by a skin biopsy. Patients must not have used steroids for at least four weeks before the diagnostic skin biopsy.
- There must be concordant agreement that skin biopsies confirmed MF by the local site dermato-pathologist and the dermatopathologist at the lead site (Fox Chase Cancer Center), utilizing the histologic criteria previously employed in clinical trials for MF and the diagnostic algorithm for defining early MF developed by the International Society for Cutaneous Lymphoma (ISCL). Patients enrolled at Fox Chase Cancer Center had their biopsies reviewed by the dermatopathologist at Stanford University.
- Patients must have been treated previously with at least one skin-directed therapy for MF including PUVA, UVB, corticosteroids, but not NM within the last two years, or topical carmustine (BCNU).
- Laboratory values must fall within the range of normal limits for the participating institution unless the principal investigator felt they were not clinically relevant.
- Patients must be free of serious concurrent illness.
- Patients must be willing and able to give informed consent, comply with study instructions and commit to all

study visits and procedures

- Males and females of childbearing potential must be using an effective means of contraception. Females must have a negative pregnancy test.

Main exclusion criteria

- Newly diagnosed MF with no prior therapy.
- A prior history of treatment with topical NM within the last two years or topical carmustine (BCNU).
- Use of topical or systemic therapies, including corticosteroids, for MF within 4 weeks of entry in the study.
- Patients with a diagnosis of stage IIB – IV MF.
- Patients who had a history of a higher T score than T2 or a higher N score than N1.
- Patients who had radiation therapy within 1 year of study start.
- Any patient who did not agree to do all lab studies at one site.
- Pregnant or nursing females, or males and females of childbearing potential not using an effective means of contraception.
- Serious known concurrent medical illness or infection, which could potentially present a safety risk and/or prevent compliance with the requirements of the treatment program.

Treatments

Patients received their assigned treatment at the baseline visit/ subsequent visits (identified by subject and randomization numbers) from the site pharmacist or other designated unblinded personnel. The study products were:

	Investigational medicinal product	Comparator
Product	Mechlorethamine (nitrogen mustard) HCl in propylene glycol (PG) gel, 0.02% strength	Chlormethine compounded in Aquaphor (AP) ointment 0.02% strength
Dose and mode of administration	Daily application of a thin topical film at approximately the same time each day, not to wash off for a minimum of 4 hours and not to cover the areas of application for 5-10 minutes. Patients were treated in an outpatient setting. Patients with stage IA disease were generally instructed to treat all affected lesions. Full body application (excluded the area around the eyes and mucous membranes) was generally prescribed if the subject had either (1) stage IB or IIA MF or (2) severity of new lesions developing after treatment initiation met the criteria for progressive disease (≥25% worsening). The final decision to treat specific lesions or whole body was at the discretion of the investigator. Treatment Adjustments for Toxicity: Frequency of application was adjusted for toxicity. The frequency of application could be reduced or temporarily suspended, then re-introduced with a reduced frequency, in case of Grade 3 - 4 skin toxicity/local dermal irritation. Topical steroids (up to 1%) were permitted only for non-MF lesions.	
Duration of treatment	Once daily for up to 12 months, unless disease progression, treatment-limiting toxicity, concomitant illness, or any change in health status necessitated discontinuation of study therapy	
Criteria for termination of therapy	Grade 3 or 4 local dermal irritation that did not improve to Grade 2 or lower within 2 weeks for Grade 3 and 4 weeks for Grade 4 Positive patch test and grade 3 or 4 dermal irritation Concurrent illness which prevented further treatment or required protocol-prohibited therapy General or specific changes in the patient's condition, including progressive disease, which in the judgment of the investigator rendered the patient unacceptable for further study treatment, or was in the patient's best interest Non-compliance for ≥28 days Patient decision to withdraw	
Usage	Patients were reminded to return all empty containers and any unused study drug at their next scheduled visit. The total usage was estimated by calculating the total number of returned used tubes/ total days on study drug.	
Follow up	Patients were followed off study for an additional 12 months to assess the potential for the development of cutaneous tumours, in particular squamous cell carcinomas.	

If patients suffered toxicity, the frequency of application was adjusted according to the protocol-defined guidelines Table 3.

Table 3: Treatment adjustments for toxicity

Type and Degree of Toxicity	Treatment Adjustments
Local Dermal Irritation	
Grade 0, 1 or 2 (Graded per NCI Criteria)[4]	No action required; observation; treatment continues.
Grade 3*	Treatment frequency should be reduced or suspended for up to two (2) weeks. If irritation improves to Grade 2 or lower, and treatment is restarted, treatment frequency may be increased every week as tolerated. Patient should be patch tested no sooner than one (1) week off treatment. Positive patch test associated with Grade 3 reactions- treatment is discontinued and patient withdrawn.
Grade 4**	Treatment must be discontinued until irritation improves to Grade 2 or lower (this must occur within four (4) weeks); treatment may then be restarted at <QD for at least one (1) week before increasing frequency, as tolerated. Treatment should not be restarted if Grade 4 toxicity occurred at <QD. Positive patch test associated with Grade 4 reactions- treatment is discontinued and patient withdrawn.
Systemic Toxicity (Graded per NCI Criteria)	Should a systemic adverse event occur that is thought to be possibly or more related to the study drug administration and possibly treatment-limiting, the Principal Investigator should be notified immediately.
*Grade 3 (Moderately Severe)-very red, with edema and vesiculation **Grade 4 (Severe)-deep red, swelling and edema with bullae formation and necrosis.	

Objectives

The primary objective: To evaluate the efficacy of topical application of nitrogen mustard (NM) 0.02% in a propylene glycol ointment (PG) vs. NM 0.02% in an Aquaphor ointment (AP) in subjects with stage I or IIA mycosis fungoides (MF).

The secondary objective: To evaluate the tolerability and safety of topical application of NM 0.02% ointment formulations in patients with stage IA, IB or IIA MF.

Outcomes / endpoints

The primary efficacy endpoint was response rate defined as response rate (complete + partial) using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS requires scoring of up to five index lesions (lesions selected for assessment of efficacy) for scaling (0–8), erythema (0–8), plaque elevation (0–3), and surface area (0–18). The sum of the scores for each of these categories and each of the five index lesions represents the total CAILS score. [70]

[70] Olsen EA, et al. Clinical End Points and Response Criteria in MycosisFungoides and Sezary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, theUnited 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.

Table 4: Composite assessment of index lesion severity

Clinical Sign and Degree or Size (scale of 0-8)	Index Lesion 1	2	3	4	5
Erythema					
Scaling					
Plaque elevation					
Hypo- or hyperpigmentation					
Lesion size*					
Subtotal					
Total (sum of subtotals)					

NOTE. Cannot be used as skin assessment in global response score. Suggestions for improvement include using actual size of lesion versus categorical score for size and eliminating pigmentation as a clinical parameter.
*Lesion size (cm^2): 0: no measurable area; 1: > 0 to ≤ 4; 2: > 4 to ≤ 10; 3: > 10 to ≤ 16; 4: > 16 to ≤ 25; 5: > 25 to ≤ 35; 6: > 35 to ≤ 45; 7: > 45 to ≤ 55; 8: > 55 to ≤ 70; 9: > 70 to ≤ 90; 10: > 90 to ≤ 110; 11: > 110 to ≤ 130; 12: > 130 to ≤ 155; 13: > 155 to ≤ 180; 14: > 180 to ≤ 210; 15: > 210 to ≤ 240; 16: > 240 to ≤ 270; 17: > 270 to ≤ 300; 18: > 300.

The CAILS score utilised in Studies 201 and 202 differed slightly from previously published versions. The assessment of hypo/hyperpigmentation was eliminated from the scale as well as the assessment of plaque elevation was simplified into a more compressed scale because the available data did not support the ability to clinically differentiate smaller gradations. There was also the substitution of the percent BSA value for index lesions rather than a 0-18 categorical scale. A comparison of these CAILS scores is shown in Table 5.

Table 5: Comparison of CAILS used in Study 201 to literature descriptions

CAILS Component	Duvic 2001a[71]	Study 201	Olsen 2011
Scaling	0–8	0–8	0–8
Erythema	0–8	0–8	0–8
Plaque elevation (mm)	0–8	0–3	0–8
Index lesion surface area	0–18	0–18	Recommends use of BSA
Hypo/hyper-pigmentation	0–8	Eliminated	Recommends elimination

BSA = body surface area.

The main secondary endpoint was as follows:

- Severity Weighted Assessment Tool (SWAT) [70] was determined by weighting BSA involvement for patches, plaques and tumours, and summing the scores for each category. The SWAT score is the sum of (1 × patch %BSA) + (2 × plaque %BSA) + (3 × tumour/ulcer %BSA).

[71] Duvic M, Martin AG, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001;137:581-593.

Response rate defined as ≥50% improvement in the SWAT 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, 3=tumour).Response was defined as ≥50% improvement in the baseline SWAT score on two or more consecutive observations over at least 4 weeks.

Table 6: Response categories for CAILS and SWAT in the clinical studies

Outcome	Change from Baseline
Response	
Complete Response (CR)	Score of zero
Partial Response (PR)	≥ 50% reduction from baseline but non-zero
Non-Response	
Stable Disease (SD)	< 50% reduction or < 25% increase from baseline
Progressive Disease (PD)	≥ 25% increase from baseline score
Unevaluable	No post-baseline data available
CR = Complete Response; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease	

Other secondary endpoints are as follows:

- % of total body surface area response rate defined as change in the percent of total body surface area involved, a component of the SWAT, as a measure of extent of cutaneous disease. Confirmed by two or more consecutive observations over at least 4 weeks.
- Time to first confirmed CAILS response defined as time to first confirmed response for a given patient, defined as the time interval from the first day study drug was dispensed to the time of the first confirmed response. This is the date of the evaluation at least 28 days after the first assessment of complete or partial response which shows that the response was sustained for at least that period of time with no intervening assessments indicating otherwise.
- Duration of response (CAILS score) defined as time from the first appearance of the response to the first assessment where the response is no longer apparent.
- Time to disease progression defined as time from first day study medication was applied to the date the first disease progression occurred (≥ 25% increase from baseline CAILS score)
- Safety: All patients who received at least one dose of study medication. AEs, physical examination, and clinical laboratory data
- PK: Plasma samples were collected to determine/ detect any levels of chlormethine.

Sample size

The required sample size to demonstrate non-inferiority was estimated to be 250 patients. This was based on assumptions that the response rate in the AP comparator arm would be approximately 68% for patients who completed at least 6 months of therapy (Efficacy Evaluable population; no major protocol violations). It was considered that approximately 25% of patients would not complete 6 months of therapy e.g. due to dermatitis, concomitant illnesses.

Randomisation

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 assessments were blinded to the assigned treatment.

Statistical methods

This trial is designed as a **non-inferiority study** comparing the PG formulation of NM, 0.02% to the AP formulation of NM, 0.02% in the treatment of Stage I and IIA mycosis fungoides. The two treatment arms were compared with respect to the response rate defined as ≥50% improvement in baseline Composite Assessment of Index Lesion Severity (CAILS) score during the 12 month study, confirmed at the next visit that is at least four weeks later (primary endpoint). Non-inferiority was assessed based on the 95% confidence interval around the ratio of the response rate of the patients treated with the PG formulation to the response rate of the patients treated with the AP formulation using the likelihood ratio methods of Miettinen and Nurminen. The PG formulation will be determined to be non-inferior to the AP formulation if the lower limit of the 95% confidence interval is ≥0.75. Based on the response of a placebo controlled trial[72], where placebo response rate was 24% (95%CI:12.6%, 38.8%), the estimated effect size of 68% for chlormethine exceeds the placebo effect of 24% and its upper limit of the 95%CI (51%). All statistical tests of primary endpoint were 2-sided with significance level of 0.05. No interim analysis was planned or conducted. Time to event parameters were estimated using Kaplan-Meier (KM) methodology and treatment arms compared using a log-rank statistic.

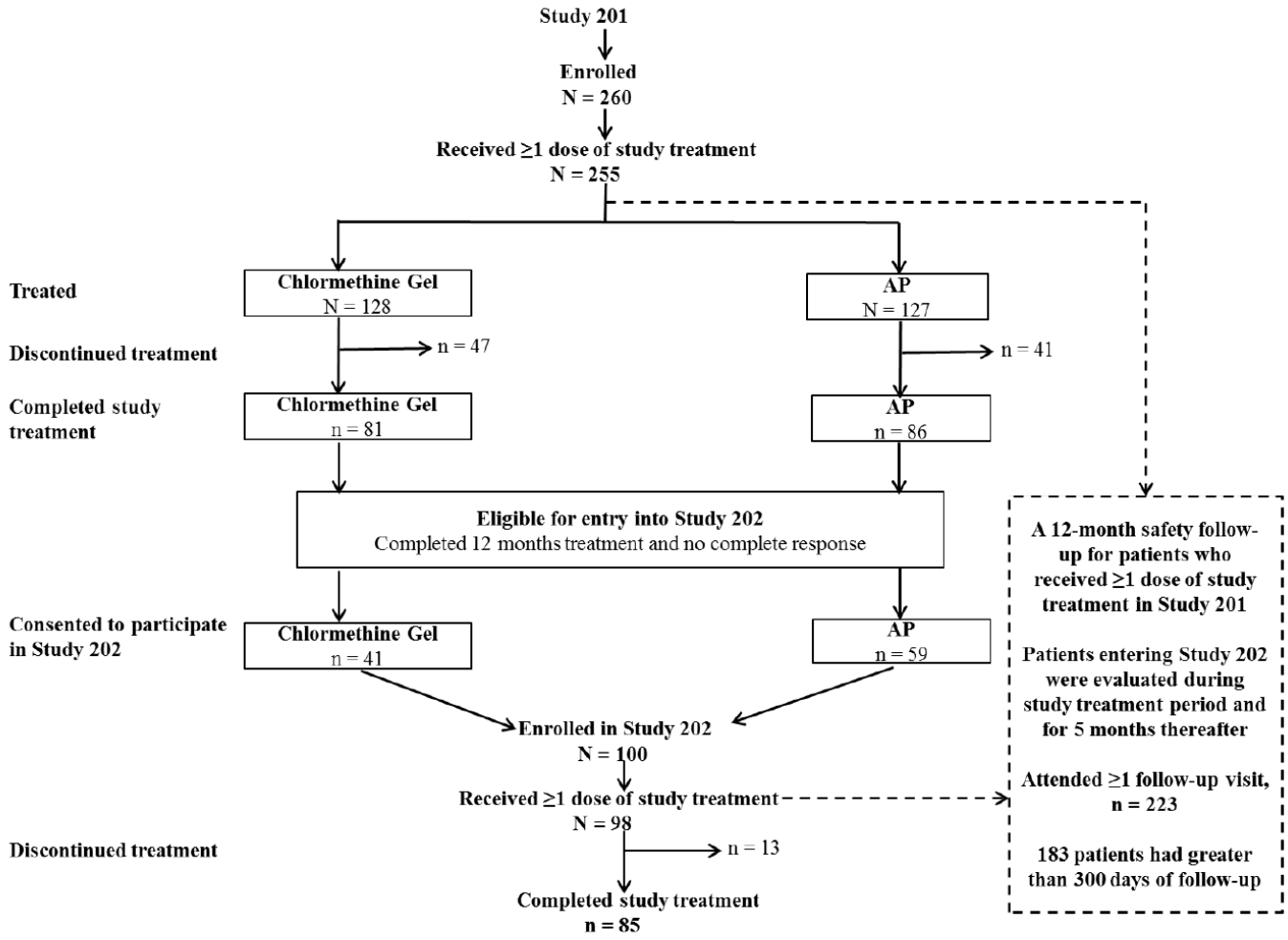
As secondary measures of efficacy, the response rates, defined as ≥50% improvement from baseline score confirmed at the next visit that is at least 4 weeks later, was compared between the two treatment arms based on the SWAT and the percent of total body surface area affected (%BSA). Additional secondary endpoints in the SAP were time to first confirmed response, duration of first confirmed response, and the time to initial disease progression based on the CAILS score. To control the Type I error, differences in secondary endpoints were tested at the 0.01 level.

The response categories for CAILS and SWAT in the clinical studies are shown in Table 6. All responses were assessed at the patient level and were to be confirmed at least 4 weeks after the first assessment (confirmed response).

Results

Participant flow

[72] Duvic M, Olsen EA, Omura GA, Maize JC, Vonderheid EC, Elmets CA et al. A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-CELL lymphoma. J Am Acad Dermatol.44(6):940-47.



AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment

Figure 2: Patients disposition in the chlormethine gel development program

A total of 260 patients were enrolled, 130 randomized to each treatment arm.

- 255 patients (98.1%) of patients received at least one application of study medication
- 62% of the gel arm patients and 66% of the AP arm patients completed the 12 month study
- A total of 88 patients withdrew prior to completing 12 months of treatment

Table 7: Patient disposition

Analysis set	Chlormethine Gel	AP	Total
Patients enrolled	130	130	260
Never treated	2	3	5*
Withdrawn from study Rx prior to completing 12 month assessment	47	41	88
Completed 12 months study Rx	81 (62%)	86 (66%)	167
*4 patients had disease that progressed between screening and baseline and were no longer eligible for the trial and 1 randomised patient withdrew consent prior to starting the study drug.			

The reasons for early withdrawal for the 93 patients (88 treated and 5 untreated) are shown in Table 8.

Table 8: Reasons for early withdrawal from the study

Reason for Withdrawal: n (%)	Chlormethine Gel	AP
Treatment Limiting Toxicity TLT)	21 (16.2)	16 (12.3)
Other Adverse Event	5 (3.8)	6 (4.6)
Lack of Efficacy	4 (3.1)	4 (3.1)
Subject's Best Interest	2 (1.5)	2 (1.5)
Concurrent Illness	4 (3.1)	3 (2.3)
Withdrew Consent	3 (2.3)	4 (3.1)
Non-Compliance	2 (1.5)	3 (2.3)
Lost to Follow-up	4 (3.1)	3 (2.3)
Other	4 (3.1)	3 (2.3)
Total	49 (37.7)	44 (33.8)

Recruitment

The study duration was 4 years. The date of first patient enrolment: May 2006 and date of last completed: July 2010.

Conduct of the study

There were two significant changes to the supply of chlormethine gel during the study:

- Instruction to patients to store the gel in the refrigerator rather than at room temperature, once dispensed (made after approximately one third of patients had completed the study)
- Introduction of gel produced on a commercial scale at the intended commercial facility.

There were also a number of protocol amendments, including:

- Follow-up period was extended to 12 months to capture the occurrence of skin cancer
- The sample size was increased from 90-110 patients to 240-250 patients in recognition that the response rates in the Efficacy Evaluable population using the CAILS score would be expected to be closer to 70% than 84%. To achieve this sample size, the number of clinical sites was increased to 13.
- The requirement for mid- and post-treatment skin biopsies was eliminated. In recognition of this the FDA requested that the designation of complete (pathologic) response be deleted from the protocol.
- There had to be concordance on the diagnosis of early MF between the local and coordinating dermatopathologist (Fox Chase Cancer Center)
- Prior topical nitrogen mustard was permitted if at least 2 years had elapsed
- The language in the protocol was clarified for:
    - No other treatments for MF were permitted
    - Prior BCNU was not permitted
- The SAP was revised to control for the Type I error rate for secondary endpoints as well as incorporate changes based on other protocol amendments.

The majority of exclusions in the EE data set (75 patients) were due to the protocol deviations at the one study site (18 patients) and skin toxicity (39 patients).

The major protocol deviations that occurred were related to randomisation.

Randomisation

The pharmacist at the site #7 assigned treatments assigned to patients based on their MF Stage and not on the master list. A total of 18 patients were recruited at this site (6.9% of patients enrolled). When it was discovered, this protocol violation was reviewed with the investigator, who was unblinded. At this time, 6 patients were still on treatment. Failure to randomise patients in accordance with the protocol was considered to be a major protocol violation. Sensitivity analyses have been introduced to evaluate the impact of this issue.

Concomitant therapy

The records of all patients who had corticosteroids listed as a concomitant medicine while receiving study therapy were reviewed. The review showed that no patient met the criterion for a major protocol violation. One AP arm patient was treated with UVB 3 days prior to the last visit, but 2 weeks after the last application of topical chlormethine gel and subsequently withdrew from the study prior to month 2 due to TLT and wasn't excluded from the EE data set.

Baseline data

Table 9: Demographic and other baseline characteristics: ITT including site #7

Characteristic	chlormethine gel (N=130) n (%)	AP (N=130) n (%)
Demographics		
Male	77 (59.2)	77 (59.2)
Female	53 (40.8)	53 (40.8)
Caucasian	97 (74.6)	96 (73.8)
Afro-American	16 (12.3)	19 (14.6)
Other	17 (13.1)	15 (11.5)
<18 years	0 (0.0)	1 (0.8)
18-64 years	93 (71.5)	86 (66.2)
65-74 years	29 (22.3)	33 (25.4)
≥75 years	8 (6.2)	10 (7.7)
Disease characteristics		
Time From Initial Diagnosis <6 months	47 (36.2)	45 (34.6)
6 months-1 year	18 (13.8)	22 (16.9)
1 year- 2 years	14 (10.8)	13 (10.0)
≥2 years	51 (39.2)	50 (38.5)

Prior MF Therapies* Corticosteroids	112 (86.1)	113 (86.9)
Phototherapy	50 (38.5)	53 (40.8)
Targretin (bexarotene)	23 (17.7)	23 (17.7)
Topical NM (>2yrs from study)	16 (12.3)	13 (10.0)
Interferons	3 (2.3)	5 (3.8)
Methotrexate	3 (2.3)	3 (2.3)
Radiation	3 (2.3)	2 (1.5)
Other*	14 (10.8)	34 (26.2)
MF Stage Stratum 1 - Stage IA	76 (58.5)	65 (50.0)
Stratum 2	54 (41.5)	65 (50.0)
Stage IB	52 (40.0)	63 (48.5)
Stage IIA	2 (1.5)	2 (1.5)
Baseline CAILS Score Mean (±SD)	37.3 (17.54)	37.4 (17.56)
Median (range)	34 (2,79)	34 (6,87)
Baseline SWAT Score Mean (± SD)	14.4 (15.87)	19.2 (20.58)
Median(range)	9.0 (1,104)	11.0 (1,104)
Baseline % BSA Mean (±SD)	12.1 (11.78)	16.6 (17.19)
Median (range)	8.0 (1,61)	10.0 (1,90)
*Patients could have more than 1 prior therapy. “Other” includes primarily emollients, anti-bacterials, anti-fungals, and retinoids other than Targretin		

Numbers analysed

Table 10: Number analysed

Analysis set	Chlormethine Gel	AP	Total
Patients enrolled	130	130	260
Patients in ITT Analysis Set	130	130	260
Patients in ITT excluding Site #7 Analysis Set	119	123	242
Patients in EE Analysis Set	90	95	185

Table 11: Description of patient population analysed

Data Sets	Description	n
ITT	All patients enrolled into the trial (Including site #7 patients as treated and not randomized in accordance with the protocol).	260
ITT excluding Site #7	All patients randomized per protocol, except those at the #7 site.	242
Efficacy Evaluable (EE)	Patients who received at least 6 months of treatment and who did not have any major protocol deviation (also excludes site #7 patients).	185 90-gel 95-AP
Exclusions from the EE	Protocol violations - 18 patients enrolled at site #7 Withdrawal prior to 6 months • Skin toxicity 20-gel; 19-AP (15% of total patients) • Never received drug 2-gel; 3-AP • Lack of efficacy 0-gel; 1-AP • Concurrent illness 3-gel; 0-AP • Withdrew consent 2-gel; 0-AP • Subject's best interest 1-gel; 0-AP • Non-compliance 1-PG; 3-AP • Other 0-gel; 2-AP	75 40-gel 35-AP

Outcomes and estimation

The primary endpoint efficacy analyses were conducted on the Intent-to-Treat (ITT), the Efficacy Evaluable (EE) populations (patients with no major protocol violations who were on study for at least 6 months) and an analysis for the ITT excluding mis-randomised subjects from the site #7. The results are presented in Table 12.

Primary endpoint: Confirmed CAILS

Table 12: Primary efficacy endpoint, confirmed CAILS response rates for Study 201 (EE, ITT, and ITT excluding Site #7 analysis sets)

Analysis set	CAILS Response Rate (%)		Ratio	
	Chlormethine gel	AP	Gel/AP	95% CI
EE	N=90	N=95		
Overall (CR+PR) n (%)	69 (76.7)	56 (58.9)	1.301	1.065–1.609
Complete Response (CR)	17 (18.9)	14 (14.7)		
Partial Response (PR)	52 (57.8)	42 (44.2)		
No response	21 (23.3)	39 (41.1)		
Stable Disease	19 (21.1)	39 (41.1)		
Progressive Disease	2 (2.2)	0 (0.0)		
ITT	N=130	N=130		
Overall (CR+PR) n (%)	76 (58.5)	62 (47.7)	1.226	0.974–1.552
Complete Response (CR)	18 (13.8)	15 (11.5)		
Partial Response (PR)	58 (44.6)	47 (36.2)		
No response	54 (41.5)	68 (52.3)		
Stable Disease	42 (32.3)	61 (46.9)		
Progressive Disease	5 (3.8)	3 (2.3)		
Unevaluable *	7 (5.4)	4 (3.1)		
ITT excluding Site #7	N=119	N=123	1.244	0.983–1.582
Overall (CR+PR) n (%)	71 (59.7)	59 (48.0)		
Complete Response (CR)	17 (14.3)	14 (11.4)		
Partial Response (PR)	54 (45.4)	45 (36.6)		
No response	48 (40.3)	64 (52.0)		
Stable Disease	36 (30.3)	59 (48.0)		
Progressive Disease	5 (4.2)	1 (0.8)		
Unevaluable	7 (5.9)	4 (3.3)		

AP = Chlormethine HCl 0.02% compounded in Aquaphor ointment, CAILS = Composite assessment of index lesion severity, CI = confidence interval, CR = Complete Response, EE = efficacy evaluable, ITT = intention-to-treat, PR = Partial Response. *Unevaluable includes 5 patients who never received study drug and 6 patients who were withdrawn without any post-baseline assessment (mainly TLT).

Efficacy results - Secondary endpoints

Confirmed SWAT response rate

Confirmed SWAT response rate was a key secondary efficacy endpoint. Response was defined as ≥50% improvement in the baseline SWAT score on two or more consecutive observations over at least 4 weeks.

Table 13: Confirmed SWAT response rates for Study 201 (EE, ITT, and ITT excluding Site #7 analysis sets)

Analysis set	SWAT Response Rates (%)			
	Chlormethine gel	AP	Ratio Gel/AP	95% CI
EE	N=90	N=95		
Overall (CR+PR) n (%)	57 (63.3)	53 (55.8)	1.135	0.893-1.448
Complete Response (CR)	8 (8.9)	4 (4.2)		
Partial Response (PR)	49 (54.4)	49 (51.6)		
No response	33 (36.7)	42 (44.2)		
ITT	N=130	N=130		
Overall (CR+PR) n (%)	61 (46.9)	60 (46.2)	1.017	0.783-1.321
Complete Response (CR)	9 (6.9)	4 (3.1)		
Partial Response (PR)	52 (40.0)	56 (43.1)		
No responses	69 (53.1)	70 (53.8)		
ITT excluding Site #7	N=119	N=123		
Overall (CR+PR) n (%)	59 (49.6)	57 (46.3)	1.070	0.882-1.394
Complete Response (CR)	8 (6.7)	4 (3.3)		
Partial Response (PR)	51 (42.9)	53 (43.1)		
No response	60 (50.4)	66 (53.7)		

AP = Chlormethine HCl 0.02% compounded in Aquaphor ointment, CI = confidence interval, CR = Complete Response, EE = efficacy evaluable, ITT = intention-to-treat, PR = Partial Response, SWAT = Severity Weighted Assessment Tool

Percentage body surface area (%BSA) - extent of cutaneous disease

The total percentage of body surface area component of the SWAT score calculation was used as a measure of the overall extent of cutaneous disease.

Table 14: Total percentage of body surface area

%BSA Response	**Chlormethine gel**	**AP**
ITT: Ratio of response was 1.036 (95% CI: 0.786–1.366)		
Responders	58 (44.6)	56 (43.1)
Non-Responders	72 (55.4)	74 (56.9)
ITT excluding site #7: Ratio of response rate was 1.092 (95% CI: 0.826-1.446)		
Responders	56 (47.1)	53 (43.1)
Non-Responders	63 (52.9)	70 (56.9)
EE: Ratio of response rate is 1.140 (95% CI: 0.883-1.478)		
Responders	54 (60.0)	50 (52.6)
Non-Responders	36 (40.0)	45 (47.4)

Time to first confirmed response based on CAILS score

The time to first CAILS confirmed response for a given patient was defined as the time interval from the first day of study drug was dispensed to the time of the first confirmed response.

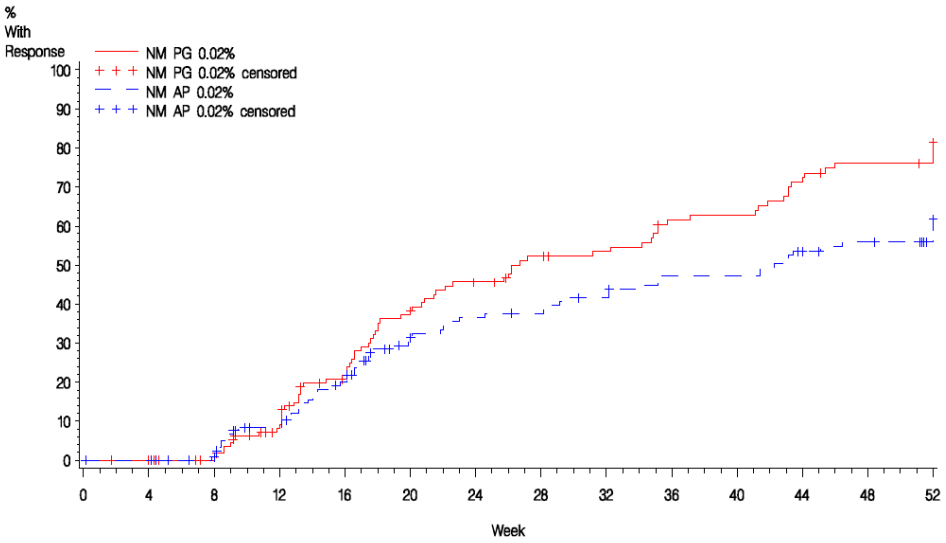


Figure 3: Time to first confirmed CAILS response (ITT Analysis set) - Study 201

NM AP = Chlormethine HCl 0.02% compounded in Aquaphor ointment, NM PG = Chlormethine gel

Duration of response based on CAILS score

For patients who achieved a confirmed CAILS response, the duration of response was defined as the time from the first appearance of the confirmed response to the first assessment where the response was no longer apparent (i.e., the CAILS score showed < 50% improvement from baseline).

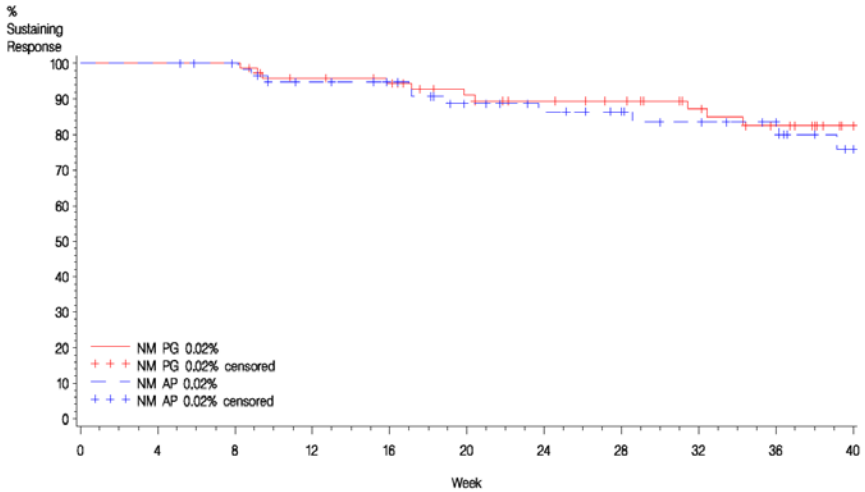


Figure 4: Kaplan-Meier Curve of Duration of Response from CAILS Assessment by Treatment Group: ITT including site #7

Time to progression based on CAILS Score

Time to disease progression was defined as time to the first ≥ 25% increase from baseline CAILS score. 15 patients randomised to chlormethine gel arm and 10 patients randomised to the AP arm had a ≥ 25% increase from baseline CAILS score at some time during the study (protocol-defined disease progression). However, the

majority of patients remained on treatment and 7 of the patients on the gel arm who stayed on treatment achieved a confirmed response.

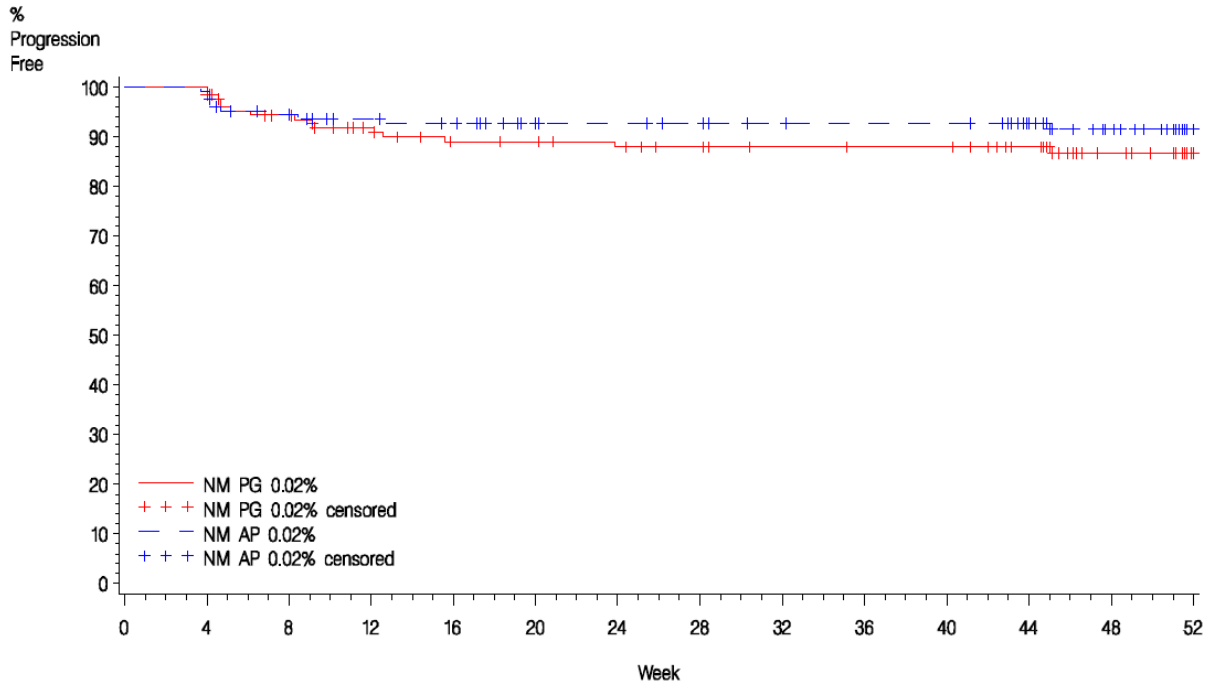


Figure 5: Time to progression (ITT including site #7)

Ancillary analyses

Across the different subgroups, the response ratio (chlormethine gel/ AP) was near 1 or exceeded 1 (favouring chlormethine gel), (see Table below) consistent with the overall study results. In addition, in all subgroups, the 95% CIs for response ratio overlapped those observed in the overall population.

Table 15: Confirmed CAILS responses by age, sex, race and MF-type CTCL stage - Study 201 (EE analysis set)

CAILS Response	Chlormethine Gel (N=90)	AP (N=95)	Ratio Gel/AP	95% CI
Age group, n/N (%)				
< 18	0/0 (0.0)	0/1 (0.0)	NC	NC
18 to 64	54/69 (78.3)	40/69 (58.0)	1.350	1.072 to 1.738
≥ 65	15/21 (71.4)	16/25 (64.0)	1.116	0.724 to 1.711
Sex, n/N (%)				
Male	38/49 (77.6)	31/53 (58.5)	1.326	1.012 to 1.775
Female	31/41 (75.6)	25/42 (59.5)	1.270	0.938 to 1.764
Race, n/N (%)				
Caucasian	51/64 (79.7)	41/67 (61.2)	1.302	1.041 to 1.661
African-American	10/14 (71.4)	7/16 (43.8)	1.633	0.857 to 3.311
Other	8/12 (66.7)	8/12 (66.7)	1.000	0.532 to 1.881
MF-type CTCL stage at Baseline, n/N (%)				
IA	39/49 (79.6)	23/41 (56.1)	1.419	1.063 to 1.989
IB, IIA	30/41 (73.2)	33/54 (61.1)	1.197	0.892 to 1.604

AP = Chlormethine HCl 0.02% compounded in Aquaphor® ointment, CAILS = Composite Assessment of Index Lesion Severity, CI = confidence interval, MF-type CTCL = mycosis fungoides-type cutaneous T-cell lymphoma, NC = not calculated.

Table 16: Confirmed CAILS responses by age, sex, race and MF-type CTCL stage - Study 201 (ITT analysis set)

CAILS Response	Chlormethine Gel (N=130)	AP (N=130)	Ratio Gel/AP	95% CI
Age group, n/N (%)				
< 18	0/0 (0.0)	0/1 (0.0)	NC	NC
18 to 64	61/93 (65.6)	44/86 (51.2)	1.282	0.999 to 1.669
≥ 65	15/37 (40.5)	18/43 (41.9)	0.968	0.566 to 1.634
Sex, n/N (%)				
Male	41/77 (53.2)	35/77 (45.5)	1.171	0.849 to 1.627
Female	35/53 (66.0)	27/53 (50.9)	1.296	0.937 to 1.827
Race, n/N (%)				
Caucasian	54/97 (55.7)	44/96 (45.8)	1.215	0.919 to 1.618
African-American	11/16 (68.8)	8/19 (42.1)	1.633	0.877 to 3.187
Other	11/17 (64.7)	10/15 (66.7)	0.971	0.567 to 1.692
MF-type CTCL stage at Baseline, n/N (%)				
IA	45/76 (59.2)	26/65 (40.0)	1.480	1.053 to 2.135
IB, IIA	31/54 (57.4)	36/65 (55.4)	1.037	0.747 to 1.425

AP = Chlormethine HCl 0.02% compounded in Aquaphor® ointment, CAILS = Composite Assessment of Index Lesion Severity, CI = confidence interval, ITT = intention-to-treat, MF-type CTCL = mycosis fungoides-type cutaneous T-cell lymphoma, NC = not calculated.

Table 17: SWAT responses by stage - Study 201

Stage	Analysis set	Chlormethine Gel	AP	Ratio Gel / AP[a]	95% CI[a]
IA	EE	57.1	48.8	1.171	0.793 - 1.776
	ITT	40.8	36.9	1.105	0.731 - 1.690
	ITT excluding Site #7	44.6	37.5	1.190	0.786 - 1.816
IB, IIA	EE	70.7	61.1	1.157	0.854 - 1.559
	ITT	55.6	55.4	1.003	0.718 - 1.386
	ITT excluding Site #7	55.6	55.9	0.993	0.708 - 1.385

[a] Derived post-hoc using the same methods as for the primary analysis of the overall SWAT response.
AP = Chlormethine HCl 0.02% compounded in Aquaphor® ointment, CI = confidence interval, EE = efficacy evaluable, ITT = intention-to-treat; SWAT = Severity Weighted Assessment Tool.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for trial Study 201

Title: A PHASE II PIVOTAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF NITROGEN MUSTARD (chlormethine) 0.02% OINTMENT FORMULATIONS IN PATIENTS WITH STAGE I OR IIA MYCOSIS FUNGOIDES (MF)			
Study identifier	**2005NMMF-201-US**		
Design	Multi-center, randomized, third party (observer) blinded study		
	Duration of main phase:		Date of First Enrollment: MAY 2006 Date of Last Completed: JUL 2010
Hypothesis	Non-inferiority		
Treatments groups	PG		Chlormethine Gel 0.02%, 12 months
	AP		Chlormethine 0.02% compounded in Aquaphor 0.02%, 12 months
Endpoints and definitions	Primary endpoint	Confirmed CAILS response rate	≥50% improvement in the baseline Composite Assessment of Index Lesion Severity (CAILS) score confirmed at least 4 weeks after

	Secondary endpoint	Confirmed SWAT response rate	⩾50% improvement in the Severity Weighted Assessment Tool (SWAT), on two or more consecutive observations over at least 4 weeks
	Secondary endpoint	Confirmed %BSA response rate	Change in the percent of total body surface area involved, a component of the SWAT, as a measure of extent of cutaneous disease confirmed at least 4 weeks after
	Secondary endpoint	Time to first confirmed CAILS response	Time to first confirmed response for a given patient, defined as the time interval from the first day study drug was dispensed to the time of the first confirmed response.
	Secondary endpoint	Duration of response	Duration of response based on CAILS score, defined as time from the first appearance of the confirmed CAILS response to the first assessment where the response is no longer apparent
	Secondary endpoint	Time to progression	Time to progression based on the CAILS score defined as time to first disease progression occurred (⩾ 25% increase from baseline CAILS score).
Database lock	01 June 2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy Evaluable		
Descriptive statistics and estimate variability	Treatment group	Ledaga (Chlormethine Gel 0.02%)	AP
	Number of subject	90	95
	CAILS (Overall CR+PR, n(%))	69 (76.7%)	56 (58.9%)
	SWAT (Overall CR+PR, n(%))	57 (63.3%)	53 (55.8%)

	%BSA (Responder n/N (%))	54/90 (60.0%)	50/95 (52.6%)
Effect estimate per comparison	Primary endpoint: CAILS	Comparison groups	Ledaga vs. AP
		Ratio	1.301
		95%CI	1.065 – 1.609
	Secondary endpoint: SWAT	Comparison groups	Ledaga vs. AP
		Ratio	1.135
		95%CI	0.893 – 1.448
	Secondary endpoint: Responder %BSA	Comparison groups	Ledaga vs. AP
		Ratio	1.140
		95%CI	0.883 – 1.478
Notes	The IIT and ITT-excluding-site#7 analyses are in line with the PP analyses.		

Supportive study

Study 2007NMMF-202-US (Study 202)

Study design

Study 202 was an open-label, multi-center, 7-month extension of Study 201 to evaluate the safety and efficacy of higher dosage strengths of Ledaga, i.e. chlormethine gel 0.04% in patients who had completed up to 12 months of treatment with chlormethine gel or AP without achieving a complete response. Patients who entered Study 202 were followed and evaluated for adverse events and skin cancers during the 7-month study treatment period and for 5 months thereafter (or the remainder of the 12-month safety follow-up period of Study 201, if treatment was discontinued prematurely).

The primary efficacy endpoint was the proportion of patients with a response (≥ 50% reduction in the baseline CAILS score of Study 202), confirmed by two or more consecutive observations over at least 4 weeks. Secondary efficacy endpoints were ≥ 50% improvement from baseline in the SWAT score, %BSA change from baseline and time to CAILS response by KM.

All analyses were conducted using the Safety analysis set (N = 98), which included all patients who received at least one application of chlormethine gel 0.04%.

Table 19: Patient disposition - Study 202 (Safety analysis set)

	Prior study treatment in Study 201		
Patient disposition	Chlormethine Gel	AP	Chlormethine gel 0.04% (N=98), n (%)
Consented			100
Treated	40	58	98 (100)
Completed treatment	37	48	85 (86.7)
Prematurely withdrawn from study[a]	3	10	13 (13.3)
Treatment-limiting toxicity	0	2	2 (2.0)
Other AE	1	1	2 (2.0)
Concurrent illness	1	0	1 (1.0)
Lack of efficacy	0	3	3 (3.1)
Non-compliance	0	2	2 (2.0)
Lost to follow-up	0	1	1 (1.0)
Other[b]	1[b]	1[c]	2 (2.0)

AE = adverse event, AP = Chlormethine HCl 0.02% compounded in Aquaphor® ointment, AE = adverse event, CAILS = composite assessment of index lesion severity.

[a] Patients were counted once under their primary reason for withdrawal.

[b] Two patients were withdrawn for other reasons. Patient 009-00024 initiated treatment with Chlormethine gel 0.04%, but had a CAILS score of 0 at the end of Study 201with a subsequent biopsy that confirmed a complete response. She was withdrawn after one month since she did not meet the eligibility criteria. Patient 012-00054 had a dispensing error at the Month 6 visit.

Primary endpoint

CAILS responses for “Prior Index Lesions” (i.e., index lesions that were used to assess efficacy in Study 201) were assessed both relative to the baseline scores of Study 201 and relative to the baseline scores of Study 202. CAILS responses at the end of Study 202, relative to Study 201 baseline, showed that 12.2% of patients had a complete response and 63.3% had a partial response, resulting in a confirmed overall response rate of 75.5%.

Table 20: CAILS responses from baseline of study 201 for prior index lesions – Study 202

CAILS outcome assessment[a]	Chlormethine gel 0.04% (N=98)
Prior index lesions[b], n (%)	
Complete response	12 (12.2)
Partial response	62 (63.3)
Complete or partial unconfirmed response	6 (6.1)
Stable disease	16 (16.3)
Progressive disease	2 (2.0)
Unevaluable	0 (0.0)
No baseline CAILS assessment	0 (0.0)
No post-baseline CAILS assessment	0 (0.0)
Overall confirmed response rate, %	75.5
95% CI	66.3 to 83.2
Overall response rate, %	81.6
95% CI	73.1 to 88.3

[a] Responses based on assessment of lesions compared to baseline of Study 201.
[b] Includes only lesions identified as index lesions in Study 201.
CAILS = Composite Assessment of Index Lesion Severity, CI=confidence interval.

CAILS responses relative to the Study 202 baseline showed that 10.2% of patients had a complete response and 13.3% had a partial response, resulting in a confirmed response rate of 23.5%. CAILS responses for "All Index Lesions" (i.e., Prior Index Lesions still present at baseline of Study 202 and new lesions that were identified as index lesions upon entry into Study 202 but were already present at baseline of Study 201) were assessed by comparison with the Study 202 baseline score only. The confirmed overall response rate was 26.5%, with 6.1% of patients showing a complete response and 20.4% showing a partial response.

Table 21: CAILS responses from baseline - Study 202

CAILS outcome assessment[a]	Chlormethine gel 0.04% (N=98)
Prior index lesions[b], n (%)	
Complete response	10 (10.2)
Partial response	13 (13.3)
Complete or partial unconfirmed response	13 (13.3)
Stable disease	49 (50.0)
Progressive disease	10 (10.2)
Unevaluable	3 (3.1)
No baseline CAILS assessment	0 (0.0)
No post-baseline CAILS assessment[c]	3 (3.1)
Overall confirmed response rate, %	23.5
95% CI	15.9–32.5
Overall response rate, %	36.7
95% CI	27.7–46.6
All index lesions[d], n (%)	
Complete response	6 (6.1)
Partial response	20 (20.4)
Complete or partial unconfirmed response	14 (14.3)
Stable disease	52 (53.1)
Progressive disease	5 (5.1)
Unevaluable	1 (1.0)
No baseline CAILS assessment	0 (0.0)
No post-baseline CAILS assessment[c]	1 (1.0)
Overall confirmed response rate, %	26.5
95% CI	18.6–35.9
Overall response rate, %	40.8
95% CI	31.5–50.7

[a] Responses based on assessment of lesions at baseline of Study 202.
[b] Includes only lesions identified as index lesions in Study 201.
[c] For prior index lesions, no post-baseline assessment occurred for Patients 002-0021-4, 009-0002-4, and 011-0015-4. Patients 002-0021-4 and 011-0015-4 had post-baseline assessments for all index lesions. Patient 009-0002-4 was withdrawn after 1 month because she had a CR at baseline. For all index lesions, Patient 009-0002-4 had no post-baseline assessment because she was withdrawn after 1 month because she had a CR at baseline.
[d] Includes all lesions identified as index lesions in Study 202.
CAILS = Composite Assessment of Index Lesion Severity, CI = confidence interval, CR = complete response.

Key secondary endpoint

Relative to the Study 201 baseline SWAT score, 4.1% of patients had a complete response and 64.3% of patients had a partial response, yielding an overall confirmed response rate of 68.4%. Relative to the Study 202 baseline SWAT score, 3.1% of patients had a complete response and 17.3% of patients had a partial response, yielding an overall confirmed response rate of 20.4%.

Table 22: SWAT responses - Study 202

SWAT Assessment[a]	Chlormethine gel 0.04% (N=98)
Comparison with baseline at entry to Study 202	
SWAT outcome assessment, n (%)	
Complete response	3 (3.1)
Partial response	17 (17.3)
Stable disease	60 (61.2)
Progressive disease	17 (17.3)
Unevaluable	1 (1.0)
No baseline SWAT assessment	0 (0.0)
No post-baseline SWAT assessment	1 (1.0)
Overall confirmed response rate, %	20.4
95% CI	13.4–29.2
Comparison with baseline at entry to Study 201	
SWAT outcome assessment, n (%)	
Complete response	4 (4.1)
Partial response	63 (64.3)
Stable disease	28 (28.6)
Progressive disease	3 (3.1)
Unevaluable	0 (0.0)
No baseline SWAT assessment	0 (0.0)
No post-baseline SWAT assessment	0 (0.0)
Overall confirmed response rate, %	68.4
95% CI	58.7–76.9

[a] SWAT response from SWAT scores at end of Study 202.
SWAT = Severity Weighted Assessment Tool, CI = confidence interval.

Secondary endpoints

SWAT responses

Confirmed responses occurred in 20.4% patients (95% CI: 13.4-29.2%). Of the 20 confirmed responses, 3.1% patients had complete responses and 17.3% had partial responses.

Discussion on clinical efficacy

Design and conduct of clinical studies

Nitrogen mustard has been part of the treatment of MF-type CTCL for more than a half century. Thus, the clinically acceptable dose of nitrogen mustard is well-known and has been well-characterised. The treatment of lesions was for the duration of the trial (maximum of 12 months), unless patients suffered treatment-limiting toxicities, which would require permanent discontinuation. If toxicity occurred, patients were required to adjust the frequency of application according to the protocol-defined guidelines (SmPC section 4.2). It has been reported in the literature that maintenance therapy has been variously continued for months, 1-2 years or

longer[73]. Patients with early MF-type CTLC stage IA, IB or IIA disease require management of the disease by application of skin-directed therapies and subsequent monitoring once the lesions have resolved. The EORTC consensus recommendations for the treatment of mycois fungoides/Sezary syndrome recommends that topical chlormethine therapy is continued for 6 months after clearance of skin lesions.[74] Therefore, it is expected that patients will be treated for as long as benefit is derived from the treatment of the skin lesions.

In addition, the application is includes two studies (study 201 andstudy 202). Study 201 is a multi-centre, randomised and observer-blinded study to support the efficacy and safety of this new pharmaceutical form. The study randomised 260 patients to the two treatment arms. Included patients have stage I or IIA MF-type CTCL, who have been treated with at least one skin-directed therapy (excl. nitrogen mustard and carmustine, which is a mustard gas-related nitrosourea compound). Both the inclusion and exclusion criteria are acceptable.

The treatment of chlormethine in the proposed indication is fully acceptable from a clinical point of view as the trial is comparing different pharmaceutical forms for an indication that has been previously approved for the active substance. Current first-line standard of care of MF-type CTCL stage I and IIA is skin-directed therapies, such as topical steroids, psoralens + PUVA, UVB and topical cystostatic agents (mechlorethamine or carmustine). The chlormethine control group used in the pivotal study is acceptable to establish efficacy and safety of Ledaga, and the activity observed for the control group was in the range of what has been reported for chlormethine formulations in clinical trials.

The principal objective of study 201 was to evaluate the efficacy of topical application of nitrogen mustard (NM) 0.02% in a propylene glycol ointment (PG) vs. NM 0.02% in an Aquaphor ointment (AP) in subjects with stage I or IIA mycosis fungoides (MF). The primary endpoint (CAILS) and several secondary endpoints (SWAT, %BSA, time to first comfirmed response, duration of response and time to progression) were considered acceptable. The primary endpoint is well-known and has previously been used as one of two co-primary endpoints in the approval of Targretin by the CHMP in 2001. The CAILS score utilised in Studies 201 and 202 differed slightly from previously published versions (see methods section). SWAT is fully acceptable as a secondary endpoint and supports the primary endpoint in the interpretation of data, as it involves direct assessment of the body surface area of each MF-type CTCL lesion. The study was designed as a non-inferiority study which is considered to be acceptable for this hybrid application. The protocol-defined criteria for non-inferiority was the lower limit of the 95% confidence interval for the ratio of the overall response rate for chlormethine Gel / AP ≥ 0.75. The chosen non-inferiority margin of 0.75 was selected to ensure that the efficacy of chlormethine gel would be greater than the historical placebo response rate. Based on the results of Study 201 the conclusion of the non-inferiority would have been reached with more conservative margins.

With regard to the conduct of the study, seven major amendments were made to the protocol during the study, and they are all considered reasonable and thus endorsed. There were no major concerns raised on the conduct of the study or major non-compliance issues revealed during the assessment of the dossier. There was a breach of randomisation at site #7. The applicant has taken account of the breach at the site #7 site in the analyses sets of the primary and secondary endpoints and it was concluded that there is no statistical difference between the data with or without the site and the results are consistent with the outcome of the primary endpoint. Study 201 appears to be a well-conducted study with an acceptable study design to support the demonstration of non-inferior clinical efficacy relative to the AP formulation in the selected MF patients population.

[73] Lindahl LM, Fenger-Gron M, Iversen 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 2014; 170:699-704

[74] Trautinger et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Se´zary syndrome. Eur J Cancer 2006: 42:1014-1030

The baseline characteristics are well balanced, however, there are slightly more patients with stage IA disease in the chlormethine gel group, however, it is not considered to have a major impact on the results. Very few patients were stage IIA (only two in each arm). Most patients are 18-64 years, have stage IA or IB disease, with prior therapy consisting of corticosteroids, phototherapy or Targretin.

Efficacy data and additional analyses

The efficacy data derived from Study 201 demonstrate that the gel formulation is non-inferior to the comparatorfor both ITT and EE populations for the primary endpoint CAILS response and for the important secondary endpoint, SWAT. For the EE analysis set, the overall response rates were 76.7% for chlormethine gel and 58.9% for AP comparator (ratio 1.301; 95% CI: 1.065–1.609). The SWAT results demonstrated an overall response rate of 63.3% for gel vs 55.8% for the AP in the EE analysis set (ratio 1.135; 95% CI: 0.893–1.448). There are slightly more patients with stage IA in the chlormethine gel arm, which appear to fair better than those with more advanced disease. Time to first confirmed response based on CAILS scores (a secondary endpoint), also showed a statistically significant difference in favour of chlormethine gel. The difference is only borderline significant in the EE analysis, while non-significant in the ITT analyses. The expected response rate for the AP formulation is within the range of responses observed in other studies with other compounded presentations of chlormethine. Therefore, the differences observed between Ledaga and the AP comparator are not considered clinically relevant and comparable equivalence can be considered demonstrated.

Additional supportive evidence is shown in study 202. Increasing the dose and extending the treatment period seems to increase the chances for complete or partial response, when compared to baseline index lesions at study start in study 201. However, the chances for partial responses diminish substantially, when compared to index lesion at study start in study 202. This study is considered to be supportive only- as the strength is higher than the proposed marketed product.

The indication ‘ topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF type CTCL) in adult patients’ is broader than the inclusion criteria of study 201 (early stage I or IIA disease and previously treated with at least one skin-directed therapy). Although the claimed indication represents a broader population of patients than the inclusion criteria of the pivotal study, no relevant differences in efficacy and safety are expected. Safety and efficacy of Ledaga are considered established for treatment of patients at any stage of the disease.

Conclusions on clinical efficacy

The formulation of chlormethine (AP) used in the pivotal trial is considered to be comparable in terms of efficacy to the reference product, based on the known pharmacokinetics of the products and given that the two products have the same active substance, strength, route of administration and indication, and based on indirect comparison of the efficacy and safety profiles.

Based on the non-inferiority in efficacy of Ledaga compared to the formulation of chlormethine used in the pivotal trial, the CHMP considered that the results of appropriate clinical trials have been submitted to demonstrate efficacy of Ledaga. These results are supported by the secondary endpoints as well as the results from the extension study 202. No additional toxicological, pharmacological or clinical tests were considered necessary to establish the efficacy of Ledaga.

2.4.7. Clinical safety

Safety data are derived from studies 2005NMMF-201-US and 2005NMMF-202-US. 255 patients were enrolled in study 2005NMMF-201-US, 128 on the chlormethine gel and 127 on AP formulation. Approximately 65% of patients received study treatment for > 48 weeks. The median duration of treatment for the gel was 51.7 weeks and 52.0 weeks for the AP. Safety information is also provided from the published literature, based on the known safety profile of the reference product and post-marketing experience in the US. Safety topics of special interest were identified as non-melanoma skin cancer, hypersensitivity and adverse events that could indicate systemic effects of topical administration of chlormethine.

Patient exposure

Patient exposure includes:

- 255 patients in study 201, (128 on chlormethine gel, 127 on AP)
- 98 patients in study 202, 90.8% patients received more than 24 weeks of treatment
- Chlormethine gel has been approved in the US under the brand name Valchlor. 4 quarterly Periodic Adverse Drug Experience Reports have been submitted to the FDA (23 August 2013 to 22 August 2014 - total of 784 patients)

Table 23: Duration of Exposure by Treatment Group and dose reductions - Study 201 (Safety Population)

Exposure in Weeks	Chlormethine gel 0.02% (N=128) n(%)	AP 0.02% (N=127) n(%)	All Subjects (N=255) n(%)
N	128	127	255
Mean (SD)	39.3 (19.34)	41.5 (17.60)	40.4 (18.49)
Median	51.7	52.0	51.9
By Range of Weeks, n (%)			
> 0 to 4	5 (3.9)	4 (3.1)	9 (3.5)
> 4 to 8	14 (10.9)	7 (5.5)	21 (8.2)
> 8 to 12	7 (5.5)	3 (2.4)	10 (3.9)
> 48	81 (63.3)	84 (66.1)	165 (64.7)
The duration of exposure is from the date of study treatment first dispensed to date of last study treatment			
Reductions in Dosing Frequency: None	99 (77.3)	112 (88.2)	211 (82.7)
Any	29 (22.7)	15 (11.8)	44 (17.3)
1 Reduction in Dosing Frequency	21 (16.4)	12 (9.4)	33 (12.9)

2 Reductions in Dosing Frequency	8 (6.3)	3 (2.4)	11 (4.3)
Temporary Suspensions None	84 (65.6)	102 (80.3)	186 (72.9)
Any	44 (34.4)	25 (19.7)	69 (27.1)
Permanent Suspension due to TLT/Other AE: None	102 (79.7)	105 (82.7)	207 (81.2)
Any	26 (20.3)	22 (17.3)	48 (18.8)

In Study 202, patients were treated for an average of 28.8 weeks and a total of 89 (90.8%) patients received > 24 weeks of treatment. 8.2% of patients required a reduction in dosing frequency, 5.1% of patients required a temporary suspension of dosing and 5.1% of patients discontinued study treatment due to AEs.

Adverse events

In study 201, 84.4% of patients treated with chlormethine gel and 90.6% of patients treated with AP experienced at least one AE. AEs that were considered to be possibly, probably, or definitely related to study drug were reported by 62% of the patients on the gel arm and 50% of patients on the AP arm. In both treatment arms, the majority of AEs were associated with the skin, with the most frequently reported AEs:

- Dermatitis (54.7% on chlormethine gel, 57.5% on AP)
- Pruritus (20.3% on chlormethine gel, 16.5% on AP)
- Skin infections (11.7% on chlormethine gel, 11.0% on AP)

Table 24: Summary of all adverse events - Study 201 (Safety analysis set)

Evaluation n (%)	Ledaga (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Patients with AEs	108 (84.4)	115 (90.6)	223 (87.5)
Adverse events	505	483	988
Subjects with drug-related adverse events	79 (61.7)	64 (50.4)	143 (56.1)
Drug-related AEs	206	160	366
Patients with SAEs	14 (10.9)	11 (8.7)	25 (9.8)
Patients with AEs as primary reason leading to discontinuation of study treatment	26 (20.3)	22 (17.3)	48 (18.8)
All patients with AEs leading to discontinuation of study treatment	28 (21.9)	23 (18.1)	51 (20.0)
Deaths	1 (0.8)	0 (0.0)	1 (0.4)
AE = adverse event, AP = chlormethine HCl 0.02% compounded in Aquaphor ointment, SAE = serious adverse event			

Table 25: Adverse events occurring in ≥2% of patients in either treatment arm, by modified SOC and preferred term - Study 201 (Safety analysis set)

Modified SOC MedDRA Preferred Term, n (%)	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Any Adverse Event	108 (84.4)	115 (90.6)	223 (87.5)
Skin and subcutaneous tissue disorders	**94 (73.4)**	**89 (70.1)**	**183 (71.8)**
Dermatitis	70 (54.7)	73 (57.5)	143 (56.1)
Pruritus	26 (20.3)	21 (16.5)	47 (18.4)
Skin infections	15 (11.7)	14 (11.0)	29 (11.4)
Skin hyperpigmentation	7 (5.5)	9 (7.1)	16 (6.3)
Skin ulceration or blistering	8 (6.3)	5 (3.9)	13 (5.1)
Actinic keratosis	5 (3.9)	2 (1.6)	7 (2.7)
Other preferred terms < 2%[b]	11 (8.6)	9 (7.1)	20 (7.8)
Respiratory, thoracic and mediastinal disorders	**26 (20.3)**	**26 (20.5)**	**52 (20.4)**
Upper respiratory tract infection	11 (8.6)	10 (7.9)	21 (8.2)
Nasopharyngitis	1 (0.8)	6 (4.7)	7 (2.7)
Influenza	2 (1.6)	4 (3.1)	6 (2.4)
Cough	3 (2.3)	3 (2.4)	6 (2.4)
Pharyngolaryngeal pain	3 (2.3)	3 (2.4)	6 (2.4)
Bronchitis	2 (1.6)	3 (2.4)	5 (2.0)
Dyspnoea	4 (3.1)	0 (0.0)	4 (1.6)
Pneumonia	3 (2.3)	0 (0.0)	3 (1.2)
Other preferred terms < 2%[b]	7 (5.5)	7 (5.5)	14 (5.5)
General disorders	**21 (16.4)**	**18 (14.2)**	**39 (15.3)**
Fatigue	3 (2.3)	6 (4.7)	9 (3.5)
Influenza like illness	2 (1.6)	3 (2.4)	5 (2.0)
Pyrexia	3 (2.3)	2 (1.6)	5 (2.0)
Pain	1 (0.8)	3 (2.4)	4 (1.6)
Oedema	3 (2.3)	1 (0.8)	4 (1.6)
Xerosis	3 (2.3)	0 (0.0)	3 (1.2)
Other preferred terms < 2%[b]	10 (7.8)	8 (6.3)	18 (7.1)
Infections and infestations	**16 (12.5)**	**20 (15.7)**	**36 (14.1)**

Sinusitis	6 (4.7)	3 (2.4)	9 (3.5)
Urinary tract infection	4 (3.1)	2 (1.6)	6 (2.4)
Fungal infection	0 (0.0)	3 (2.4)	3 (1.2)
Other preferred terms < 2% [b]	8 (6.3)	13 (10.2)	21 (8.2)
Gastrointestinal disorders	**21 (16.4)**	**14 (11.0)**	**35 (13.7)**
Nausea	6 (4.7)	3 (2.4)	9 (3.5)
Diarrhoea	4 (3.1)	3 (2.4)	7 (2.7)
Abdominal pain	3 (2.3)	1 (0.8)	4 (1.6)
Other preferred terms < 2% [b]	9 (7.0)	9 (7.1)	18 (7.1)
Musculoskeletal and connective tissue disorders	**11 (8.6)**	**16 (12.6)**	**27 (10.6)**
Arthralgia	5 (3.9)	3 (2.4)	8 (3.1)
Back pain	5 (3.9)	2 (1.6)	7 (2.7)
Other preferred terms < 2% [b]	4 (3.1)	12 (9.4)	16 (6.3)
Nervous system disorder	**10 (7.8)**	**15 (11.8)**	**25 (9.8)**
Headache	4 (3.1)	5 (3.9)	9 (3.5)
Dizziness	2 (1.6)	3 (2.4)	5 (2.0)
Paraesthesia	1 (0.8)	3 (2.4)	4 (1.6)
Carpal tunnel syndrome	0 (0.0)	3 (2.4)	3 (1.2)
Other preferred terms < 2% [b]	6 (4.7)	8 (6.3)	14 (5.5)
Injury, poisoning and procedural complications	**9 (7.0)**	**11 (8.7)**	**20 (7.8)**
Excoriation	0 (0.0)	3 (2.4)	3 (1.2)
Other preferred terms < 2% [b]	9 (7.0)	8 (6.3)	17 (6.7)
Neoplasms benign (incl cysts and polyps)	**6 (4.7)**	**8 (6.3)**	**14 (5.5)**
Cyst	3 (2.3)	1 (0.8)	4 (1.6)
Other preferred terms < 2% [b]	4 (3.1)	8 (6.3)	12 (4.7)
Neoplasms malignant	**3 (2.3)**	**7 (5.5)**	**10 (3.9)**
Basal cell carcinoma	2 (1.6)	4 (3.1)	6 (2.4)
Other preferred terms < 2% [b]	2 (1.6)	4 (3.1)	6 (2.4)
Blood and lymphatic system disorders	**3 (2.3)**	**6 (4.7)**	**9 (3.5)**
Lymphadenopathy	1 (0.8)	4 (3.1)	5 (2.0)

Other preferred terms < 2% [b]	2 (1.6)	2 (1.6)	4 (1.6)
Immune system disorders	**3 (2.3)**	**6 (4.7)**	**9 (3.5)**
Hypersensitivity	3 (2.3)	2 (1.6)	5 (2.0)
Drug hypersensitivity	0 (0.0)	3 (2.4)	3 (1.2)
Other preferred terms < 2% [b]	0 (0.0)	1 (0.8)	1 (0.4)
Any other class <2%[c]	**31 (24.2)**	**29 (22.8)**	**60 (23.5)**

AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

a: Post-hoc analysis with pooling and re-coding of preferred terms as described in Table 35.

b: Preferred terms with an incidence < 2% were pooled under 'Other preferred terms'.

c: SOCs with an incidence < 2% were pooled under 'Any other class'.

For Study 202, skin and subcutaneous tissue disorders were the most frequently reported AEs (53.1% [dermatitis 48.0%]). No cases of hypersensitivity were reported. 6.1% experienced at least one SAE, although none were considered to be related to study treatment. No deaths occurred in the study or within 30 days of stopping study treatment.

Table 26: Summary of all adverse events - Study 202 (Safety analysis set)

Evaluation	Prior Study Treatment group		
	Chlormethine Gel (N=40) n(%)	AP (N=58) n(%)	Chlormethine gel 0.04% (N=98) n (%)
Patients with AE	24 (60.0)	47 (81.0)	71 (72.4)
Patients with SAE	2 (5.0)	4 (6.9)	6 (6.1)
Patients with AE leading to discontinuation of study treatment	2 (5.0)	3 (5.2)	5 (5.1)
Deaths occurring during study	0 (0.0)	0 (0.0)	0 (0.0)
AE = adverse event, AP = chlormethine HCl 0.02% compounded in Aquaphor ointment, SAE = serious adverse event			

Table 27: Adverse events occurring in ≥2% of all patients, by modified SOC and MedDRA preferred term - Study 202 (Safety analysis set)

	Prior Study Treatment in Study 201		
Modified SOC MedDRA Preferred Term	Chlormethine Gel (N=40) n (%)	AP (N=58) n (%)	Chlormethine gel 0.04% (N=98) n (%)
Any Adverse Event	24 (60.0)	47 (81.0)	71 (72.4)
Skin and subcutaneous tissue disorders	**18 (45.0)**	**34 (58.6)**	**52 (53.1)**
Dermatitis	15 (37.5)	32 (55.2)	47 (48.0)
Pruritus	2 (5.0)	6 (10.3)	8 (8.2)
Skin infections	3 (7.5)	4 (6.9)	7 (7.1)
Skin hyperpigmentation	1 (2.5)	3 (5.2)	4 (4.1)
Actinic keratosis	0 (0.0)	2 (3.4)	2 (2.0)
Skin papilloma	0 (0.0)	2 (3.4)	2 (2.0)
Other preferred terms <2%[b]	0 (0.0)	1 (1.7)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	**7 (17.5)**	**11 (19.0)**	**18 (18.4)**
Bronchitis	1 (2.5)	3 (5.2)	4 (4.1)
Upper respiratory tract infection	3 (7.5)	1 (1.7)	4 (4.1)
Cough	0 (0.0)	2 (3.4)	2 (2.0)
Nasal congestion	0 (0.0)	2 (3.4)	2 (2.0)
Nasopharyngitis	0 (0.0)	2 (3.4)	2 (2.0)
Pharyngolaryngeal pain	1 (2.5)	1 (1.7)	2 (2.0)
Rhinitis allergic	0 (0.0)	2 (3.4)	2 (2.0)
Other preferred terms <2%[b]	3 (7.5)	2 (3.4)	5 (5.1)
Musculoskeletal and connective tissue disorders	**3 (7.5)**	**6 (10.3)**	**9 (9.2)**
Pain in extremity	1 (2.5)	1 (1.7)	2 (2.0)
Other preferred terms <2%[b]	2 (5.0)	5 (8.6)	7 (7.1)
Gastrointestinal disorders	**2 (5.0)**	**5 (8.6)**	**7 (7.1)**
Diarrhoea	0 (0.0)	2 (3.4)	2 (2.0)
Nausea	0 (0.0)	2 (3.4)	2 (2.0)
Other preferred terms <2%[b]	2 (5.0)	4 (6.9)	6 (6.1)
Infections and infestations	**3 (7.5)**	**3 (5.2)**	**6 (6.1)**
Herpes simplex	1 (2.5)	1 (1.7)	2 (2.0)
Other preferred terms <2%[b]	2 (5.0)	2 (3.4)	4 (4.1)

Injury, poisoning and procedural complications	**1 (2.5)**	**5 (8.6)**	**6 (6.1)**
Contusion	0 (0.0)	2 (3.4)	2 (2.0)
Other preferred terms <2% [b]	1 (2.5)	5 (8.6)	6 (6.1)
Blood and lymphatic system disorders	**1 (2.5)**	**2 (3.4)**	**3 (3.1)**
Lymphadenopathy	0 (0.0)	2 (3.4)	2 (2.0)
Other preferred terms <2% [b]	1 (2.5)	0 (0.0)	1 (1.0)
Any other class <2% [c]			
Other preferred terms <2% [b]	6 (15.0)	12 (20.7)	18 (18.4)

AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

a: Post-hoc analysis with pooling and re-coding of preferred terms as described in Table 35.

b: Preferred terms with an incidence < 2% were pooled under 'Other preferred terms'.

c: SOCs with an incidence < 2% were pooled under 'Any other class'.

Severity of Adverse Drug Reactions

Table 28: Summary of adverse drug reactions for chlormethine by modified preferred term (re-coded), according to severity - Study 201

MedDRA Preferred Term	NOT REPORTED		MILD		MODERATE		MODERATELY SEVERE		SEVERE		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Selected Preferred terms												
Total patients with at least one ADR	-		30	23.4%	24	18.8%	33	25.8%	3	2.3%	90	70.3%
Dermatitis	-		23	18.0%	20	15.6%	25	19.5%	2	1.6%	70	54.7%
Pruritus	-		12	9.4%	9	7.0%	4	3.1%	1	0.8%	26	20.3%
Skin infections	-		10	7.8%	2	1.6%	1	0.8%	2	1.6%	15	11.7%
Skin ulceration or blistering	-		4	3.1%	-		3	2.3%	1	0.8%	8	6.3%
Hypersensitivity	-		-		-		2	1.6%	1	0.8%	3	2.3%

A patient having experienced the same event (preferred term) more than once is counted only once for that ADR.
ADR = adverse drug reaction

Table 29: Summary of adverse drug reactions for aquaphor by modified preferred term (re-coded), according to severity - Study 201

MedDRA Preferred Term	NOT REPORTED No.	%	MILD No.	%	MODERATE No.	%	MODERATELY SEVERE No.	%	SEVERE No.	%	TOTAL No.	%
Selected Preferred terms												
Total patients with at least one ADR	-		41	32.3%	22	17.3%	21	16.5%	2	1.6%	86	67.7%
Dermatitis	-		34	26.8%	19	15.0%	20	15.7%	-		73	57.5%
Pruritus	-		10	7.9%	9	7.1%	1	0.8%	1	0.8%	21	16.5%
Skin infections	-		10	7.9%	2	1.6%	1	0.8%	1	0.8%	14	11.0%
Skin ulceration or blistering	1	0.8%	2	1.6%	2	1.6%	-		-		5	3.9%
Hypersensitivity	-		-		-		2	1.6%	-		2	1.6%

A patient having experienced the same event (preferred term) more than once is counted only once for that ADR.
ADR = adverse drug reaction

Table 30: Severity of drug-related skin and subcutaneous AEs

Local Dermal Irritation N (%)	PG					AP				
	Grade 0 None	Grade 1 Mild	Grade 2 Mod	Grade 3 Mod Severe	Grade 4 Severe	Grade 0 None	Grade 1 Mild	Grade 2 Mod	Grade 3 Mod Severe	Grade 4 Severe
	52 (40.7)	22 (17.2)	18 (14.1)	33 (25.8)	3 (2.3)	71 (55.9)	21 (16.5)	13 (10.2)	21 (16.5)	1 (0.8)

Skin and subcutaneous disorders were the most frequently reported moderately severe AEs (25.8% in the gel arm vs. 16.5% in the AP arm).

The causality to the topical use of chlormethine gel can be established only for the following skin-related ADRs: dermatitis, pruritus, skin infections, skin hyperpigmentation and skin ulceration/ blistering.

Table 31: Summary of potential adverse drug reactions, by modified SOC and preferred term - Study 201 (Safety analysis set)

Modified SOC Preferred Term	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Skin and subcutaneous tissue disorders AEs with an incidence ≥ 2% patients in either treatment group Skin and subcutaneous tissue disorders	94 (73.4)	89 (70.1)	183 (71.8)
Non-skin AEs with an excess of ≥ 3 patients in the Chlormethine Gel group Gastrointestinal disorders	6 (4.7)	3 (2.4)	9 (3.5)

Infections and infestations	6 (4.7)	3 (2.4)	9 (3.5)
Musculoskeletal and connective tissue disorders	5 (3.9)	2 (1.6)	7 (2.7)
Respiratory, thoraric and mediastinal disorders	6 (4.7)	0 (0.0)	6 (2.4)
General disorders	3 (2.3)	0 (0.0)	3 (1.2)
AE = adverse event; AP = chlormethine HCl 0.02% compounded in Aquaphor ointment; SOC = system organ class			

Table 32: Summary of serious adverse events, by modified SOC and preferred term - Study 202 (Safety analysis set)

Modified SOC MedDRA Preferred Term	Prior Study Treatment in Study 201		
	Chlormethine Gel (N=40) n (%)	AP (N=58) n (%)	Chlormethine gel 0.04% (N=98) n (%)
Any Serious Adverse Event	2 (5.0)	4 (6.9)	6 (6.1)
Cardiac disorders	1 (2.5)	1 (1.7)	2 (2.0)
Musculoskeletal and connective tissue disorders	1 (2.5)	1 (1.7)	2 (2.0)
General disorders	0 (0.0)	1 (1.7)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.5)	0 (0.0)	1 (1.0)
Reproductive system and breast disorders	0 (0.0)	1 (1.7)	1 (1.0)
AP= chlormethine HCl 0.02% compounded in Aquaphor ointment, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class.			

Adverse events of special interest

Skin cancers

Given the known mechanism of action of chlormethine, and specifically the alkylation of DNA, attention has been placed on whether treatment with topical chlormethine increases the risk for other forms of skin cancer, especially squamous cell and basal cell carcinomas. Vonderheid, in his review of the records of 331 patients, reported an estimated relative risk of 7.8 for squamous cell carcinoma and a risk of 1.8 for basal cell carcinoma [75]. Vonderheid included patients in his analysis who received concurrent skin-damaging or immunosuppressive therapies and did not evaluate a chlormethine monotherapy group separately for risk of secondary cancer development. Exposure to ultraviolet light or radiation therapy can increase risk of developing

[75] Vonderheid EC, Tan ET, Kantor AF, et al. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 1989;20:416-28.

skin cancer. In the Stanford series[76] where topical chlormethine was applied as monotherapy, non-melanoma skin cancers occurred in 8 of 203 patients; however, 6 of these 8 patients had received subsequent therapies such as psoralen UVA (PUVA) or total skin electron beam therapy prior to secondary skin cancer detection. In the 2 patients who developed skin cancer with chlormethine monotherapy, the skin cancer occurred in sites of actinic damage (face) that were not exposed to chlormethine application. The author concluded that the potential for secondary skin cancer development is increased in patients who have used multiple sequential topical skin-damaging therapies and chlormethine, but not in patients who have used chlormethine as monotherapy[76] . Similar findings were reported in an earlier publication[77] .

Secondary non-melanoma skin cancers have been reported in the [76]literature as a potential toxicity associated with chlormethine and other skin-directed therapies such as PUVA and electron beam radiation. 10 patients (3 on the gel; 7 on the AP arm) developed non-melanoma skin cancers during the study or during the 12 month follow-up period. The majority of skin cancers occurred in untreated areas.

- Squamous cell carcinoma: 5 patients (updated)
    - 2 on the gel arm (1 in an untreated area) and 3 on the AP arm (2 in an untreated area)
    - 1 AP patient, there was no MF lesion on the dorsal hand, but it could not be confirmed that the drug did not get on the dorsal hand during application
    - 1 PG patient developed a SCC in a treated area on her right upper back during the follow-up period (previous history of BCC, SCC, breast cancer and prior MF therapies included UVB and targretin)

- Basal cell carcinoma: 6 patients (updated)
    - 2 on the gel arm patients and 4 on the AP arm

[76] 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;139:165-73.
[77] Hoppe RT, Abel EA, Deneau DG, Price NM. Mycosis fungoides: management with topical nitrogen mustard. J Clin Oncol 1987;5:1796-803.

Table 33: Occurrence of non-melanoma skin cancers (including 12-month follow up period) - Study 201 and Study 202 (Safety analysis set)

Tumor type	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	Chlormethine gel 0.04% (N=98) n (%)	All Patients (N=255) n (%)
Any skin (non-melanoma) malignancy	3 (2.3)	7 (5.5)	1[a] (1.0)	11 (4.3)
Basal cell carcinoma	1 (0.8)	3 (2.4)	1 (1.0)	5 (2.0)
Squamous cell carcinoma	1 (0.8)	2 (1.6)	0 (0.0)	3 (1.2)
Merkel cell carcinoma	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Both basal cell carcinoma and squamous cell carcinoma	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.8)

AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment

a: Patient 002-0026 developed a basal cell carcinoma on her left shoulder during the 12-month follow-up period for Study 201, 80 days after completing treatment with Chlormethine gel 0.04% in Study 202. This patient had been treated with AP during Study 201. The basal cell carcinoma was in an untreated area and not considered related to study treatment by the investigator.

Hypersensitivity

Hypersensitivity reactions have been reported with topical chlormethine. Cutaneous hypersensitivity was reported for 3 patients (2.3%) in the chlormethine gel arm and 2 patients (1.6%) in the AP arm in Study 201. All cases were considered related or possibly related to study drug and triggered treatment discontinuation.

Serious adverse event/deaths/other significant events

SAEs in Study 201

25 (9.8%) patients (14 [10.9%] who received chlormethine gel; 11 [8.7%] who received AP) experienced an SAE:

- Skin and subcutaneous tissue disorders: 1 AP patient (cellulitis)
- Cardiac disorders: 1 gel patient, 4 AP patients
- Respiratory disorders: 3 gel patients and 1 AP patient
- Malignant neoplasm: 1 patient in each arm

Table 34: Summary of serious adverse events, by modified SOC and preferred term - Study 201 (Safety analysis set)

Modified SOC Preferred Term	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Any Serious Adverse Event	14 (10.9)	11 (8.7)	25 (9.8)
Cardiac disorders	**1 (0.8)**	**4 (3.1)**	**5 (2.0)**
Cardiac failure congestive	0 (0.0)	2 (1.6)	2 (0.8)
Myocardial infarction	0 (0.0)	2 (1.6)	2 (0.8)
Atrial fibrillation	1 (0.8)	0 (0.0)	1 (0.4)
Coronary artery occlusion	0 (0.0)	1 (0.8)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**3 (2.3)**	**1 (0.8)**	**4 (1.6)**
Pneumonia	2 (1.6)	0 (0.0)	2 (0.8)
Asthma	1 (0.8)	0 (0.0)	1 (0.4)
Lung disorder	0 (0.0)	1 (0.8)	1 (0.4)
Gastrointestinal disorders	**1 (0.8)**	**2 (1.6)**	**3 (1.2)**
Gastrointestinal infection	0 (0.0)	1 (0.8)	1 (0.4)
Haemorrhoids	1 (0.8)	0 (0.0)	1 (0.4)
Pancreatitis	0 (0.0)	1 (0.8)	1 (0.4)
General disorders	**2 (1.6)**	**0 (0.0)**	**2 (0.8)**
Chest discomfort	1 (0.8)	0 (0.0)	1 (0.4)
Pain	1 (0.8)	0 (0.0)	1 (0.4)
Infections and infestations	**2 (1.6)**	**0 (0.0)**	**2 (0.8)**
Appendicitis	1[a] (0.8)	0 (0.0)	1 (0.4)
Staphylococcal infection	1 (0.8)	0 (0.0)	1 (0.4)
Neoplasms malignant	**1 (0.8)**	**1 (0.8)**	**2 (0.8)**
Neuroendocrine carcinoma of the skin	0 (0.0)	1 (0.8)	1 (0.4)
Thyroid gland cancer	1 (0.8)	0 (0.0)	1 (0.4)
Nervous system disorders	**1 (0.8)**	**1 (0.8)**	**2 (0.8)**
Dizziness	0 (0.0)	1 (0.8)	1 (0.4)
Global amnesia	1 (0.8)	0 (0.0)	1 (0.4)
Vascular disorders	**2 (1.6)**	**0 (0.0)**	**2 (0.8)**
Aortic aneurysm	1 (0.8)	0 (0.0)	1 (0.4)
Cerebrovascular accident	1 (0.8)	0 (0.0)	1 (0.4)
Peripheral vascular disorder	1 (0.8)	0 (0.0)	1 (0.4)

Hepatobiliary disorders	**0 (0.0)**	**1 (0.8)**	**1 (0.4)**
Biliary colic	0 (0.0)	1 (0.8)	1 (0.4)
Reproductive system and breast disorders	**1 (0.8)**	**0 (0.0)**	**1 (0.4)**
Menorrhagia	1 (0.8)	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**1 (0.8)**	**1 (0.4)**
Cellulitis	0 (0.0)	1 (0.8)	1 (0.4)
Surgical and medical procedures	**1 (0.8)**	**0 (0.0)**	**1 (0.4)**
Parathyroidectomy	1 (0.8)	0 (0.0)	1 (0.4)

AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment, SOC = system organ class

a: A serious adverse event was submitted for Patient 002-0042 (PG) due to hospitalization for an appendectomy. His laboratory data showed grade 1 anemia and grade 2 thrombocytopenia when hospitalized. Laboratory parameters were monitored, and on 28 May he was diagnosed with myelodysplastic syndrome (MDS). MDS was considered by the investigator not to be related to Chlormethine Gel, but was secondary to extensive exposure to systemic alkylating agent and other forms of chemotherapy received for non-Hodgkin lymphoma (NHL) in the 1980s and 1990s.

Table 35: Summary of serious adverse events, by modified SOC and preferred term - Study 202 (Safety analysis set)

	Prior Study Treatment in Study 201		
Modified SOC MedDRA Preferred Term	**Chlormethine Gel (N= 40) n (%)**	**AP (N= 58) n (%)**	**Chlormethine gel 0.004% (N=98) n (%)**
Any Serious Adverse Event	2 (5.0)	4 (6.9)	6 (6.1)
Cardiac disorders	**1 (2.5)**	**1 (1.7)**	**2 (2.0)**
Aortic valve stenosis	0 (0.0)	1 (1.7)	1 (1.0)
Supraventricular tachycardia	1 (2.5)	0 (0.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	**1 (2.5)**	**1 (1.7)**	**2 (2.0)**
Arthritis	0 (0.0)	1 (1.7)	1 (1.0)
Hip fracture	1 (2.5)	0 (0.0)	1 (1.0)
General disorders	**0 (0.0)**	**1 (1.7)**	**1 (1.0)**
Non-cardiac chest pain	0 (0.0)	1 (1.7)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (2.5)**	**0 (0.0)**	**1 (1.0)**
Lung cancer metastatic	1 (2.5)	0 (0.0)	1 (1.0)
Reproductive system and breast disorders	**0 (0.0)**	**1 (1.7)**	**1 (1.0)**
Prostatitis	0 (0.0)	1 (1.7)	1 (1.0)

AP= chlormethine HCl 0.02% compounded in Aquaphor® ointment, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

Deaths

Study 201:

There was one death reported during the study, and none during the 12-month follow-up period. One patient was diagnosed with widely disseminated metastatic cancer less than 2 months after the initiation of treatment with chlormethine gel and died on Day 84 of the study.

The MRI revealed widely disseminated carcinoma (biopsy results favoured colon primary). The disseminated metastatic cancer could have been present at baseline and thus, was deemed not related to study treatment.

Study 202:

There were no deaths during the study or within 30 days of stopping study treatment. One patient died due to metastatic lung cancer 6 months after premature discontinuation of study treatment due to lung cancer. The metastatic lung cancer was considered by the investigator as unrelated to study treatment.

Laboratory findings

There are no reports of laboratory abnormalities associated with topical chlormethine use in the published literature. Clinical laboratory safety data were monitored throughout the two studies and no trend toward abnormal values were noted.

Safety in special populations

Elderly patients

In Study 201, 79 patients (31%) were ≥ 65 years of age. There was a higher frequency of AEs in elderly patients and higher proportions of elderly patients discontinued due to an AE. However, overall, drug related safety observations in the ≥ 65 years of age are consistent with the whole population.

Table 36: Adverse events by subgroup - Study 201 (Safety analysis set)

Subgroup	All AEs n/N (%)		TLT/AE Withdrawals n/N (%)	
	Chlormethine Gel	AP	Chlormethine Gel	AP
<65	74/91 (81.3)	76/85 (89.4)	12/91 (13.2)	8/85 (9.4)
≥65	34/37 (91.9)	39/42 (92.9)	14/37 (37.8)	14/42 (33.3)
Male	63/75 (84.0)	66/76 (86.8)	19/75 (25.3)	13/76 (17.1)
Female	45/53 (84.9)	49/51 (96.1)	7/53 (13.2)	9/51 (17.6)
Caucasian	85/95 (89.5)	85/93 (91.4)	21/95 (22.1)	21/93 (22.6)
African-American	10/16 (62.5)	17/19 (89.5)	2/16 (12.5)	0/19 (0.0)
Race other	13/17 (76.5)	13/15(86.7)	3/17 (17.6)	1/17 (6.7)
MF-type CTCL Stage IA	66/75 (88.0)	57/63 (90.5)	18/75 (24.0)	19/63 (30.2)
MF-type CTCL Stage IB/IIA	42/53 (79.2)	58 /64 (90.6)	8/53 (15.1)	3/64 (4.7)
AE = adverse event, AP = Chlormethine HCl 0.02% compounded in Aquaphor ointment, MF = mycosis fungoides, TLT = Treatment Limiting Toxicity Source				

Paediatric patients

Only one 11 year old patient was enrolled in the pivotal trial and completed 10 months of therapy (AP arm). The patient was withdrawn for non-compliance.

Race

No impact of race can be concluded from the presented studies.

Pregnancy and lactation

The applicant did not submit data on use in pregnancy and lactation. Study protocols for studies 201 and 202 excluded pregnant or nursing women, and all men and women of childbearing potential had to agree to use an effective method of contraception. However, the female partner of one of the male patients became pregnant approximately 1–2 months after the initiation of treatment with AP. It was reported that the outcome of the pregnancy was a healthy, full-term infant. No other reports of pregnancy in patients treated with topical chlormethine were identified in the published literature.

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies on drug-drug interactions.

Discontinuation due to adverse events

AEs leading to discontinuation of study treatment in study 201

AEs leading to discontinuation of chlormethine are well described in the published literature. More dose modifications triggered by TLTs (reduced frequency/ temporary suspensions) occurred in patients who received the gel formulation. A similar number of patients discontinued study treatment due to an AE in both treatment groups. The most frequently reported AEs were associated with skin and subcutaneous tissue disorders.

Table 37: Dose modifications and TLTs - Study 201 (Safety analysis set)

	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Reductions in dosing frequency	29 (22.7)	15 (11.8)	44 (17.3)
Temporary suspension of medication	44 (34.4)	25 (19.7)	69 (27.1)
Discontinuation due to any AE	28 (21.9)	23 (18.1)	51 (20.0)
Discontinuations meeting protocol definition of TLT	21 (16.4)	16 (12.6)	37 (14.5)

AE = adverse event, AP = chlormethine HCl 0.02% compounded in Aquaphor ointment, TLT = Treatment Limiting Toxicity

AEs leading to discontinuation of study treatment in Study 202

The most frequent reason for early withdrawal from the study was lack of efficacy, which was reported for 3 (3.1%) patients. Two (2.0%) patients each withdrew for TLT and other AEs. Of the 98 patients who were treated in Study 202, 40 had previously received treatment with chlormethine gel, and 58 had previously received treatment with the AP formulation in Study 201. Most premature withdrawals from the study in Study 202 (10/13) were for patients who had previously received the AP formulation in Study 201.

Five (5.1%) patients prematurely discontinued study treatment due to AEs: 2 patients who had previously received chlormethine gel and 3 patients who had previously received AP. Of these, 4 patients discontinued due to AEs of skin and subcutaneous tissue disorders (one patient who had previously received chlormethine gel and 3 patients who had previously received AP), and one patient discontinued due to SAEs (hip fracture and metastatic lung cancer).

Of the 4 patients who withdrew due to skin-related AEs, 2 patients experienced treatment-limiting skin toxicity requiring discontinuation from the study, as defined in the protocol, and 2 patients were discontinued due to skin AEs: one due to pruritus and one due to erythema.

Table 38: Summary of adverse events that led to discontinuation of study treatment, by modified SOC and preferred term - Study 202 (Safety analysis set)

	Prior Study Treatment in Study 201		
Modified SOC Preferred Term	Chlormethine Gel (N= 40) n (%)	AP (N= 58) n (%)	Chlormethine gel, 0.04% (N=98) n (%)
Any AE leading to premature study treatment discontinuation[a]	**2 (5.0)**	**3 (5.2)**	**5 (5.1)**
Skin and subcutaneous tissue disorders	1 (2.5)	3 (5.2)	4 (4.1)
Dermatitis contact	1 (2.5)	1 (1.7)	2 (2.0)
Dermatitis	0 (0.0)	1 (1.7)	1 (1.0)
Erythema	0 (0.0)	1 (1.7)	1 (1.0)
Pruritus	1 (2.5)	0 (0.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	1 (2.5)	0 (0.0)	1 (1.0)
Hip fracture	1 (2.5)	0 (0.0)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.5)	0 (0.0)	1 (1.0)
Lung cancer metastatic	1 (2.5)	0 (0.0)	1 (1.0)

AE = adverse event, AP= chlormethine HCl 0.02% compounde in Aquaphor® ointment, SOC = system organ class
a: Patients are categorized 'Discontinued' if the course of action following an AE includes Study Discontinuation.

AEs leading to dose modification

Few patients required dosing modifications: 8 (8.2%) patients required a temporary reduction in dosing frequency, and 5 (5.1%) patients required a temporary suspension of dosing. Dose modifications were triggered by TLTs.

2.4.8. Post marketing experience

The published experience demonstrates that the vast majority of AEs observed are related to skin and subcutaneous tissue disorders. Chlormethine 0.02% gel was approved as Valchlor in the US in August 2013. 4 quarterly Periodic Adverse Drug Experience Reports for Valchlor have been submitted to the FDA, covering the review period from 23 August 2013 to 22 August 2014. A total of 784 patients have been treated with Valchlor since approval to the 22 August 2014, and 243 reports were received including 241 cases from 222 treated patients. The remaining 2 cases were reports from care givers who experienced adverse reactions through secondary exposure (one who experienced itching after smelling the medication whilst applying the gel to the patient and the other who noticed a neck rash in the morning after her partner applied the chlormethine gel at bedtime, the night before).

The most commonly reported AEs were:

- Skin and subcutaneous tissue disorders (266 events, 45.5%)
    - Pruritus (49, 8.4%)
    - Erythema (37, 6.3%)
    - Rash (20, 3.4%)
    - Blister (18, 3.1%)
    - Skin irritation (17, 2.9%)
    - Burning sensation (13, 2.2%)
- General disorders and administration site conditions (119 events, 20.3%)
- Injury, poisoning and procedural complications (56 events, 9.6%)

2.4.9. Discussion on clinical safety aspects

The safety evaluation is based on two sponsored studies (Study 2005NMMF-201-US (Study 201) and Study 2007NMMF-202-US (Study 202)) and post-marketing data reported for Valchlor (mechlorethamine) which is marketed in the US.

The safety database included 255 patients; approximately 65% of patients were treated for more than 48 weeks in both treatment arms. Overall, the mean duration of exposure is 39.3 weeks in the chlormethine gel arm compared to 41.5 weeks in the AP arm. The median exposure time is 51.7 weeks vs. 51.9 weeks in chlormethine gel arm and AP arm, respectively. Taking into consideration the known safety and tolerability of the active substance, the safety database provides an acceptable number of exposed patients as well as exposure time to the product.

Given the lack of evidence for systemic exposure to chlormethine after topical use, non-skin related AEs such as nausea, sinusitis, back pain, dyspnoea and pneumonia were not considered to be ADRs. The following reactions have been assessed as ADRs and have been included in section 4.8 of the Ledaga SmPC: dermatitis, pruritus, skin infections, skin ulceration and blistering, skin hyperpigmentation and hypersensitivity.

The most common AEs are within the SOC “Skin and subcutaneous tissue disorders”. Dermatitis is the most commonly observed AE and was reported for 70 (54.7%) patients in the chlormethine gel arm vs. 73 in the AP arm (57.5%), with a higher incidence of moderate-moderately severe intensity in the chlormethine gel arm. The second most common AE is pruritus 20.3% vs. 16.5% in chlormethine gel arm and AP arm, respectively. These AEs are all well-known and manageable in the clinical setting. Hypersensitivity was observed in 2% (5 patients, 3 with chlormethine and 2 with AP) of patients in the study 201. Thus, local skin reactions and hypersensitivity have been included in section 4.4 of the SmPC and in the RMP as important identified risks. In addition, based on the non-clinical toxicity data and the causality of the skin-related-ADRs and severity of the AEs, contact with mucous membranes, especially those of the eyes, must be avoided. Exposure of mucous membranes such as the oral mucosa or nasal mucosa causes pain, redness, and ulceration, and these may be severe. Exposure of the eyes to chlormethine causes pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible anterior eye injury may occur (section 4.4 of the SmPC). Toxicity to mucous membranes/eyes has been included as an important identified risk.

Five (3.9%) patients experienced 9 Grade 4 AEs in the chlormethine gel arm vs. 9 (7.1%) patients with 10 Grade 4 AEs in the AP arm. Most of the Grade 4 AEs were observed in the SOC “Skin and subcutaneous tissue disorders”. Three malignant neoplasms (1 basal cell carcinoma, 1 squamous cell carcinoma, and 1 basal cell and

squamous cell carcinoma) were observed in the chlormethine gel arm compared to 7 in the AP arm (3 basal cell carcinoma, 2 squamous cell carcinoma, 1 merkel cell carcinoma and 1 basal cell/squamous cell carcinoma). However, none of the AEs were judged related to chlormethine treatment. Development of secondary skin cancers is a known risk of skin targeted therapies in the treatment MF-type CTCL. Thus, patients treated with topical chlormethine should be monitored for skin cancers, as described in section 4.4 of the proposed SmPC and skin cancers is included in the RMP as important potential risks. The ADRs in section 4.8 of the SmPC are consistent with the approved SmPC of Caryolysine (chlormethine).

As chlormethine is to be applied at home by the patient or the caregiver, there is the risk to secondary exposure to someone other than the patient, a risk which has been included in the RMP as an important potential risk. The PRAC and CHMP considered that given the risk of secondary exposure as well the severity of the toxicity to mucous membranes, educational material in the form of a patient and caregiver card (included in each box of Ledaga) was necessary in order to educate patients on all steps to be followed when applying Ledaga, to inform patients what to do in case of secondary exposure and to inform patients on the use of the transparent sealable plastic bag.

In general, there are comparable number of AEs, SAEs and AEs leading to discontinuation in the two treatment arms, with only small percentage differences, however it must be noted that the numbers are small.

There are more dose modifications in the chlormethine gel, mainly due to skin and subcutaneous tissue disorders. The guidance on dose modification in section 4.2 of the SmPC is considered adequate.

No laboratory abnormalities have been noted. This is consistent with the observation that there is no documented systemic exposure following topical administration of chlormethine gel.

There are limited data on the use of chlormethine in pregnant women. Studies in animals have shown reproductive toxicity after systemic administration (see section 5.3 of the SmPC and non-clinical discussion). Ledaga is not recommended during pregnancy (section 4.6 of the SmPC). It is unknown whether chlormethine is excreted in human milk. A risk to newborns/infants cannot be excluded due to the potential for topical or systemic exposure of the suckling infant to chlormethine through contact with the mother's skin. A decision must be made whether to discontinue breast-feeding or to discontinue Ledaga therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the breast feeding mother (section 4.6 of the SmPC). The use of Ledaga during pregnancy and lactation has been added as an important potential risk.

The safety and efficacy of Ledaga in children aged 0 to 18 years have not been established. No data are available (section 4.2 of the SmPC). Therefore, the use of chlormethine in paediatric patients has been included as missing information.

2.4.10. Conclusions on clinical safety aspects

The safety of Ledaga has been adequately characterised. The ADRs observed in the clinical trials are broadly consistent with those in the SmPC for the reference medicinal product, Caryolysine and the published literature. Post-marketing events reported to date have not identified any new risks or signals and no regulatory actions have been taken for safety reasons.

2.5. Pharmacovigilance

Risk Management Plan

Safety concerns

Table 39: Summary of the safety concerns

Important identified risks	Hypersensitivity Local skin reactions Toxicity to mucous membranes / eye
Important potential risks	Skin cancers Secondary exposure to someone other than the patient Use during pregnancy and lactation
Missing information	Use in paediatric patients Concomitant use with topical corticosteroids

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 40: Summary table of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity	Wording in SmPC section 4.3, 4.4, 4.8	None proposed.
Local skin reactions	Wording in SmPC section 4.2, 4.4, 4.8	None proposed.
Toxicity to mucous membranes / eye	Wording in SmPC section 4.4	Transparent sealable child-resistant plastic bag. Patient alert card.
Skin cancers	Wording in SmPC section 4.4, 5.3	None proposed.
Secondary exposure to someone other than the patient	Wording in SmPC section 4.2, 4.4, 6.4	Transparent sealable child-resistant plastic bag. Patient alert card.
Use during pregnancy	Wording in SmPC section 4.6, 5.3	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
and lactation		
Missing information – Use in paediatric patients	Wording in SmPC section 4.1, 4.2, 5.1	None proposed.
Missing information – Concomitant use of topical corticosteroids	Wording in SmPC section 4.2, 4.4, 5.1	None proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 (dated 15 December 2016) is acceptable.

Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.6.2. Additional monitoring

Not applicable

3. Benefit-risk balance

This application concerns a hybrid version of chlormethine for a new pharmaceutical form (gel for cutaneous use) with reference to Caryolysine (a solution for injection and cutaneous use). The indication for the product Ledaga is for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF type CTCL) in adult patients the same as for the reference medicinal product Caryolysine. Typical bioequivalence studies in plasma cannot be conducted for topical products that are not absorbed, and in any case plasma would not be a relevant compartment. This is consistent with the guidance from the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). A review of the published literature was provided for this application and considered sufficient to cover the non-clinical aspects as well as to support the clinical aspects (efficacy and safety). In addition, this application relies also on the results from a clinical trial and a follow up study comparing the commercial formulation chlormethine gel against an adequate chlormethine comparator were submitted to provide further pharmacological data (pharmacokinetics and pharmacodynamics) as well as confirm the efficacy and safety data of the product. These data demonstrate the efficacy and safety chlormethine gel, and based on indirect comparison, the efficacy and safety of the gel formulation are in line with what has been observed with the reference medicinal product in term of all important clinical endpoints.

The safety and tolerability of topical chlormethine are well known and no new concerns have been raised from the reported AEs in the safety database from the studies 201 and 202. The ADRs observed are considered well tolerated and manageable following the recommendations in the SmPC, routine PhV and implementation of additional risk minimisation activities. The PRAC and CHMP considered that educational material for patients and caregivers was necessary to ensure the safe use of the product.

Taking into account the overall evidence in terms of efficacy and safety, the data are considered robust and adequate to establish the efficacy and safety of Ledaga.

Therefore, the CHMP is of the opinion that the benefits of the product outweigh the risks and concluded that a positive benefit-risk balance has been established for Ledaga in the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ledaga is favourable in the following indication:

Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF type CTCL) in adult patients (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

In order to minimise and prevent the Important Identified Risk of “Toxicity to mucous membranes / eye “ and the Important Potential Risk of “Secondary exposure to someone other than the patient“, the MAH shall ensure that in each MS where Ledaga is marketed, following additional risk minimisation measures are fulfilled:

- Ledaga should be supplied with a transparent, sealable, child-resistant plastic bag to prevent secondary exposure and contamination when Ledaga is stored in the refrigerator:
    - Instruction on how to accurately use, open and dispose a plastic bag should be printed on the plastic bag. The MAH must agree about the content and format of the text prior to launch of Ledaga in each MS with the National Competent Authority (NCA).
    - The plastic bag should not be used for any other purposes and must be disposed after 60 days together with unused refrigerated Ledaga and any waste material, including nitrile gloves in accordance with local requirements.
- A patient alert card, sized to be included in Ledaga outer packaging, together with the Patient Information Leaflet (PIL) is provided to all patients and caregivers who are expected to administer and use Ledaga.