LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zoviduo
(acyclovir 5% and hydrocortisone 1 %)

SE/H/882/01/DC

This module reflects the scientific discussion for the approval of Zoviduo. Please note that the marketing authorisation was first approved with the name "Xerclear" and therefore this name is used throughout the document. The procedure was finalised on 14th of October 2009For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Medivir has applied for a marketing authorisation for “Xerclear, cream. The active substance is a combination of the antiviral substance acyclovir and the anti-inflammatory substance hydrocortisone. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Xerclear is presented in the form of a cream containing 50 mg/g aciclovir and 10 mg/g hydrocortisone. The excipients are Cetostearyl alcohol, Liquid paraffin, Poloxamer 188, Propylene glycol, Isopropyl myristate, Sodium lauryl sulphate, White soft paraffin, Citric acid monohydrate, Sodium hydroxide/Hydrocloric acid (for pH adjustments), and purified water. The cream is packed in aluminium laminated polyethylene plastic tube.

II.2 Drug Substance

Aciclovir has a monograph in the Ph Eur.

Aciclovir is a white to off-white, crystalline powder which is slightly soluble in water. The structure of aciclovir has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Hydrocortisone has a monograph in the Ph Eur.

Hydrocortisone is a white or almost white, crystalline powder, which is practically insoluble in water. The structure of hydrocortisone has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substances specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Xerclear cream is formulated using excipients described in the current Ph Eur or USP. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substances. The manufacturing process has been sufficiently described and critical

steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C. Do not refrigerate or freeze.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The rationale for the use of a combination acyclovir and hydrocortisone in the treatment of recurrent mucocutaneous HSV is based on that control of both the viral replication and the inflammation is expected to result in an improved efficacy. Acyclovir and hydrocortisone are well characterised substances and there is long term marketing experience with various formulations and concentrations.

III.2 Pharmacology

For the current application a limited series of pharmacology studies were performed focussed on providing data for the combination.

Acyclovir is a nucleoside analogue that is selectively converted to a triphosphate form in cells infected by herpes virus interfering with HSV DNA polymerase and inhibiting replication of viral DNA. *In vitro* acyclovir inhibits HSV-1 virus with an IC_{50} ranging from 0.1 to 0.5 µM. Viral shedding in recurrent HSV is shorter than in primary infection due to a primed immune response with most occurring during the first 8 hours after lesions begin developing followed by an inflammatory reaction that involves local infiltration of NK, CD4+ and CD8+T cells. An antiinflammatory agent would be expected to control this response and thus improve efficacy.

Hydrocortisone is a corticosteroid with immunosuppressive, vasoconstrictor and anti-inflammatory properties linked to various extents to its binding to cytoplasmic receptors present in different cell types. In view of previous reports that glucocorticoids have a potential to increase viral replication specific studies *in vitro* were conducted. In primary human embryonic lung fibroblasts (HEL) and A101D cells viral replication and viral growth was inhibited by acyclovir and neither hydrocortisone nor dexamethasone had an effect. In primary human gingival fibroblasts (HGF) an increase in viral replication occurred in cells treated with hydrocortisone or dexamethasone prior to infection with HSV-1 and this was prevented by acyclovir. Viral yield was not affected in HGF cultures when dexamethasone (or hydrocortisone) (1 µM) were added at time of infection and this was taken to indicate the effect not being direct, but rather reflecting an altered immune response. Acyclovir, acting as a chain terminator, would exert its effect down-stream such a promoter. The results are consistent with that an up regulation of HSV viral replication not occurring using the ME-609 cream and the proposed posology.

In vivo studies in a guinea pig model of primary HSV infection showed as expected that a formulation of 5% acyclovir and 1% hydrocortisone was more effective than placebo or 1% hydrocortisone alone with respect to reducing lesions score. In this model some clinical parameters were indicative of the ME-609 cream being more effective than Zovirax® while both formulations had similar effect in reducing viral shedding. Guinea pig skin is stated to

contain up to 10 times higher levels of deoxythymidine than human skin. Deoxythymidine has been shown to decrease the antiviral activity of acyclovir and so antiviral activity may be underestimated in this model.

The ME-609 was evaluated also in a model of recurrent disease; a mouse model of zosteriform HSV infection with adoptive transfer of immunity. Immunocompetent mice that had received adoptive transfer of immunity from mice infected with HSV-1 cleared virus more rapidly than naïve mice although clinical signs persisted and were more severe in similarity to the clinical disease situation. The parameters of efficacy monitored, ear thickness and zoster score indicated that treatment with the ME-609 cream had a greater effect than Zovirax® cream or 1% hydrocortisone in ME-609 vehicle. There were no relevant differences in viral titers between the Zovirax® and the ME-609 cream groups.

It may be noted that the initial unbuffered formulation had a pH of approximately 7 and was used in most non-clinical studies as well as in phase I and II clinical studies. Due to stability considerations a citric acid buffered formulation pH 5 was later developed and chosen as the final clinical formulation. In a comparative mouse study using adoptive transfer of immunity, the original formulation and a citric acid buffered pH 5 formulation were shown to have similar efficacy in terms of ear thickness reduction, zoster score and virus titers and only minor differences were reported.

Taken together with already available data, the pharmacology of the ME-609 cream is considered sufficiently addressed from the non-clinical point of view. Results from the submitted non-clinical studies overall support the effectiveness of the combination acyclovir and hydrocortisone in treatment of mucocutaneous HSV.

III.3 Pharmacokinetics

The general pharmacokinetics of acyclovir and hydrocortisone are well known and have been previously characterised. Available data indicate that neither acyclovir nor hydrocortisone are systemically absorbed to any significant extent following topical administration using a range of different formulations.

In vitro acyclovir has been shown to preferentially distribute into cells that are infected with herpesviruses. The multiplication of the herpes simplex virus takes place in the deeper layers of the epidermis. The penetration rate *in vitro* has been reported to correlate with the antiviral effect *in vivo* using the guinea-pig model. Additional studies specific to the present application were conducted to determine skin penetration of acyclovir from two cream formulation using guinea pig skin. Using full thickness skin, penetration of acyclovir from a formulation containing isopropyl myristate, similar to the intended clinical formulation, was up to 2 fold higher than from a formulation using propylene glycol as skin penetrant and believed to be essentially similar to the Zovirax® cream formulation. The study indicated that changes to the modified aqueous cream base may not adversely affect skin penetration of acyclovir. Hydrocortisone *in vivo* has shown vasoconstrictive effects and the possibility exists that this could lead to higher local concentrations of acyclovir in the skin due to reduced rate of removal into the blood stream, however, no studies to support such effects have been conducted.

The metabolic fate of acyclovir after topical absorption is not completely known. Plasma protein binding is low after intravenous administration. *In vitro*, acyclovir is metabolized mainly by intracellular phosphorylation mediated by virus encoded thymidine kinase and several cellular enzymes in cells infected with herpesviruses. Following systemic absorption,

acyclovir is excreted principally in urine. When acyclovir 5% ointment was applied topically to the intact skin of healthy adult males (5 times daily for 4 days), approximately 0.04% of the total daily dose was detected in urine. When acyclovir 5% ointment was applied topically in immunocompromised adults with localized varicella-zoster, up to 9.4% of the total daily dose of acyclovir was excreted in urine as unchanged drug within 24 hours.

It is not known if the drug or its metabolites are distributed into milk following topical application. Since systemic absorption is low, likely any distribution is of limited importance although data indicate that acyclovir is distributed into milk following oral administration, generally in concentrations greater than concurrent maternal plasma concentrations.

III.4 Toxicology

The general toxicology of acyclovir and hydrocortisone is well known and has been previously characterised. The toxicological characteristics of acyclovir can be found summarised in product labels. The compound has overall a low potential for acute toxicity by oral or intravenous administration. The main toxicity of acyclovir is coupled to adverse effects on the renal system linked to the relatively low solubility of acyclovir in the urine. A 1 year dog study reported no adverse effects at a dose of 15 mg/kg/day given orally.

Slight erythema was noted in topical irritation studies in guinea pigs, but overall the formulation appeared essentially non-irritating both on intact and abraded skin. While the formulation used in this study differed from the clinical formulation in that citric acid buffering was absent, clinical data is judged sufficient to evaluate the local tolerance of the product.

Studies on the potential for genotoxicity of acyclovir have yielded largely negative results, and high concentrations of the compound were generally required to produce a positive result or to induce sufficient cytotoxicity to make a negative result valid. The genotoxic effects are related primarily to its clastogenicity. Acyclovir is clastogenic in mammalian cells both *in vitro* and *in vivo*. It has been noted that the natural bases and their nucleosides are clastogenic at a concentration of about 1 mmol/L and that the clastogenicity of acyclovir in hamsters occurred at roughly comparable concentrations of the natural bases and their nucleosides.

The genetic changes that have been coupled to acyclovir are probably consequential to the DNA chain termination activity of acyclovir. The doses required to produce a clastogenic response were overall much higher than those relevant to the clinical or preclinical *in vivo* situation. Furthermore, in long-term carcinogenicity studies in mice and rats by gavage, no treatment-related tumours were reported.

Fertility and reproduction in mouse and rat was not impaired by acyclovir except at high doses when implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live foetuses. No testicular abnormalities were seen in dogs at doses giving systemic exposure levels over 6 times the expected clinical, but at higher doses testicular atrophy and aspermatogenesis were observed in rats and dogs. No teratogenicity was evident in mouse, rabbit or rat.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. The data is considered in product labels of acyclovir. The small size of the registry indicates that reliable or definitive conclusions regarding the safety of acyclovir

in pregnant women and their developing foetuses cannot be made at present. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Acyclovir concentrations have been documented in breast milk in 2 women following oral administration of acyclovir in Zovirax®, but topical use of the current cream formulation would not be expected to provide any measurable levels. Administration to a nursing mother should be with caution and only when indicated. Safety and effectiveness of oral formulations of acyclovir in pediatric patients younger than 2 years of age have not been established.

Hydrocortisone is a widely used compound and while formal non-clinical studies are limited the clinical experience is extensive. Systemic toxicological effects of corticosteroids are linked to adrenal suppression depending on potency, frequency of use and the formulation.

An environmental risk assessment was consistent with no increased risk for the environment from the use of the formulation.

III.5 Ecotoxicity/environmental risk assessment

An environmental risk assessment was consistent with no increased risk for the environment from the use of the formulation.

III.6 Discussion on the non-clinical aspects

Overall the scope of non-clinical studies focussed on providing data on the combination and this was considered an adequate approach also in view of the long-term marketing experience with the individual compounds. The pharmacology and general toxicology of both acyclovir and hydrocortisone are well known and have been previously characterised. Topical administration would be expected to result in limited exposure indicating no concerns for systemic toxicity. The relevant sections of the SPC acceptably reflect the data available.

IV. CLINICAL ASPECTS

Pharmacokinetics

No clinical pharmacokinetic studies have been performed which is considered acceptable due to the low total dose and expected limited exposure after topical administration of acyclovir and hydrocortisone. The hypothetical interaction between the drugs due to vasoconstriction caused by hydrocortisone would result in even lower systemic exposure to acyclovir, hence an in vivo interaction study is deemed not necessary.

Pharmacodynamics

The pharmacodynamics of the two active substances, acyclovir, 5%, and hydrocortisone, 1%, are well known. The combination is currently not routinely used for the treatment of the claimed indications, but corticosteroids have been used as an adjunct to anti-infective agents in several bacterial and fungal diseases to reduce inflammation associated with the immune response that contributes to the pathogenesis of the illness.
In a pharmacodynamic double-blind study (study No. 99-609-005) it was demonstrated that ME-609 Cream was similar to commercially available hydrocortisone (1%) cream on skin blanching (vasoconstriction) and effects on the local blood flow, as measured by laser Doppler technique.

Clinical efficacy

Clinical efficacy in subjects with RHL was addressed in four studies, one phase 2 study (proof-of -concept), one pivotal study and two supportive phase 3 studies with focus on safety in

immuno-compromised adult patients and adolescents.

Studies Addressing Efficacy and Safety of ME-609 (acyclovir, 5% and hydrocortisone, 1%) Cream

Phase	Study No.	Short Name	Study Title
2	98-609-013	Phase 2	Efficacy of acyclovir in combination with a glucocorticosteroid on UV induced herpes labialis
3	609-04	Pivotal	A randomized, double-blind, active-controlled, vehicle-controlled, subject initiated study comparing efficacy and safety of ME-609 versus acyclovir cream for treatment of recurrent herpes simplex labialis
3	609-06	Immunocompromised	A randomized, double-blind, active-controlled, subject-initiated study comparing ME-609 to acyclovir cream for treatment of recurrent herpes simplex labialis in immunocompromised patients
3	609-07	Adolescents	An open label, multi-center, phase III, subject initiated safety study of ME-609 in treatment of recurrent herpes simplex labialis in adolescents

In Study No. 98-609-013 (Phase 2), all subjects applied study treatment starting 48 hours after UVR exposure, 5 times daily. The treatment period was 6 days to ensure that all UVR-induced lesions received adequate treatment. In the Phase 3 studies, the subject self-initiated treatment at the first sign/symptom of a recurrence and then applied the treatment 5 times daily for 5 days. In all studies, only the first herpes recurrence was studied. Efficacy and safety of repeat use of ME-609 Cream were not addressed. The four studies are briefly described below:

Study ID	No. of study centres /loca-tions	Design	Study Posology	Study Objective	Subjs by arm entred/ compl.	Duration	Gender M/F Age (mean, range)	Diagnosis Incl. criteria	Primary Endpoint
98-609-013 Phase 2	4 USA & Canada	Multicenter double-blind, randomized, placebo-cont rolled, Phase 2.	ME-609 and placebo cream (ME-609 vehicle), 6x/day for up to 5 days	To compare The efficacy of ME-609 cream versus placebo cream (ME-609 vehicle) on the time to healing (loss of hard crust) of delayed classical herpes labialis (HSV) Lesions experimenttally induced after UVR exposure.	380/380 ME-609: 190/190 Placebo: 190/190	15 days	98/282 37 years (18-77)	Subjects 18 years or older with history of herpes labialis on over-exposure to sunlight in last 12 months or ≥ 2 lesions in last 12 months.	Episode duration (loss of hard crust), termed 'time to healing'.
609-04 (Pivotal) Phase 3	55 USA & Canada	Multicenter, double-blind, randomized, active cont-rolled, placebo controlled, subject initiated Phase 3	ME-609, Placebo cream (ME-609 vehicle) and Acyclovir 5% cream (in ME-609 vehicle), 5x/day for 5 days	To compare the safety and efficacy of ME-609 with acyclovir and vehicle for the treatment of herpes labialis recurrences in immunocompetent adults	ME-609: 601/582 Acyclovir :610/591 Placebo: 232/225	3 weeks	406/1037 43.8 years (18-80)	Subjects 18-80 years with a history of at least three episodes of recurrent labial herpes during the prior 12 months	Proportion of subjects with non-ulcerative herpes recurrences
609-06 (Immunoco m pro-mised) Phase 3	25 Russia & Ukraine	Multicenter, randomized, double-blind, active controlled, subject initiated, Phase 3	ME-609 and acyclovir 5% cream (in ME-609 vehicle), 5x/day for 5 days	To compare the efficacy of ME-609 cream with acyclovir 5% cream (ME-609 vehicle) by evaluating the episode duration of a herpes labialis recurrence.	ME-609: 77/75 Acyclovir: 30/29	3 weeks	58/49 31.8 years (19-64)	Immunocomp romised (mean CD4+ T-cell count 100-500/ mm3), subjects 18 years and older with a history of ≥2 herpes labialis recurrences during the prior 12 months	Episode duration (loss of hard crust) for ulcerative recurrence and from start of treatment to time of no signs or symptom for a non-ulcerative recurrence

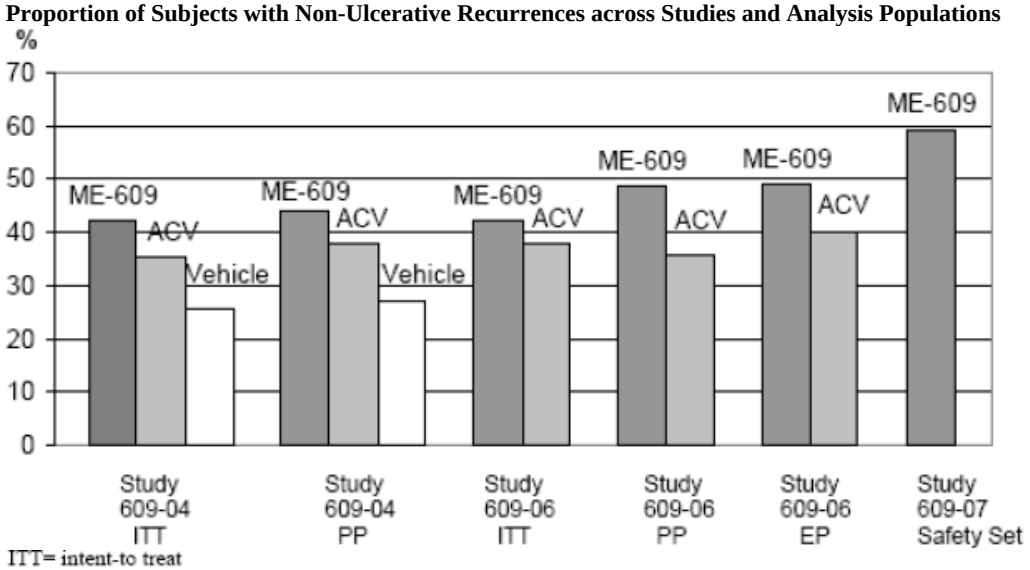
609-07 (Adole-scents) Phase 3	26 Sweden and Russia	Multicenter, Open label, Phase 3, Subject initiated study	ME-609 Topically five times daily for five days to an area at least 10 mm around the outer margin of the lesion	To determine the safety of ME-609 for the treatment of herpes labialis recurrences in adolescents	134/132	3 weeks	67/67 14.5 years (12-17)	Subjects, between 12 and 17 years old, with ≥2 herpes labialis recurrences during the prior 12 months	Recurrence Stage categorization, maximum lesion area, AEs

Demographic data and other baseline characteristics including herpes history were generally comparable between treatment groups in each study. The studied population was mainly white, predominantly female with all age groups between 12 years and the elderly (> 65 years of age) well represented. The average number of herpes recurrences during the preceding year was comparable across all studies ranging between 4 and 6 per year. Patients included in the pivotal study as well as patients in study 609-07 (adolescents) were considered representative for the target patient group.

Prevention of ulcerative lesions

In the pivotal trial (609-04) there was a higher proportion of non-ulcerative recurrences in the ME-609 Cream group (42%) as compared with acyclovir (35%, p = 0.014) and vehicle (26%, p<0.0001). The proportion of non-ulcerative recurrences in the vehicle group was within the expected background incidence. The absolute improvement was similar to the preventive effect observed in the phase 2 study. The preventive effect of ME-609 Cream was observed across age groups, including the elderly (> 65 years) and adolescents. The results from immunocompromised subjects were consistent with the findings in the pivotal study: 42% of subjects in the ME-609 Cream group and 38% in the acyclovir group experienced non-ulcerative recurrences (statistical testing not performed). Within both studies, the percentage of subjects in whom the recurrences were non-ulcerative was consistent across the ITT and per protocol (PP) analysis populations and in the evaluable population (EP) in the latter study. Recurrences were non-ulcerative in 60% of the adolescent subjects treated with ME-609 Cream. This is a strikingly high proportion, given that all but one of the recurrences was objectively confirmed by the investigators. However this was a safety study with no comparator, and therefore these data can only be regarded as indicative of a preventive effect.

Proportion of Subjects with Non-Ulcerative Recurrences across Studies and Analysis Populations



ITT= intent-to treat
PP= per protocol
EP= evaluable population

In the pivotal study, the proportion of subjects with non-ulcerative recurrences increased the earlier the treatment was started in both the ME-609 Cream and the acyclovir groups, an effect not observed in placebo-treated subjects. Regardless of the stage at which treatment was initiated, ME-609 Cream was consistently more effective than acyclovir.

Treatment Initiation Stage vs. Proportion of Non-Ulcerative Recurrences: ITT Populations [Study No. 609-04 (Pivotal) and Study No. 609-06 (Immunocompromised)]

Treatment Group	Recurrence Stage at Treatment Start			Association Between Stage at Start of Treatment and Recurrence Type (p-value)	ME-609 vs. Acyclovir (p-value)	ME-609 vs. placebo p-value
	Prodome	Erythema	Papule			
Study No. 609-04 (Pivotal)						
ME-609 [x/y (%)]	46.0 (180/391)	37.1 (59/159)	33.3 (15/45)	0.023[a]	0.011[b]	<0.0001[b]
Acyclovir [x/y (%)]	39.0 (155/397)	32.9 (54/164)	14.3 (6/42)	0.002[a]		
Placebo [x/y (%)]	30.7 (43/140)	18.9 (14/74)	20.0 (3/15)	0.077[a]		
Study No. 609-06 (Immunocompromised)						
ME-609 [x/y (%)]	60.0 (12/20)	37.0 (10/27)	43.5 (10/23)	0.305[c]	0.882[d]	NA
Acyclovir [x/y (%)]	33.3 (2/6)	44.4 (4/9)	50.0 (5/10)	0.881[c]		

a Study No. 609-04 (pivotal), Cochran-Armitage trend test.
b Study No. 609-04 (pivotal), ME-609 versus acyclovir: CMH test controlling for stage at start of treatment p = 0.011, Breslow-Day test for homogeneity p = 0.289, logistic regression p = 0.012. ME-609 versus placebo: CMH test controlling for stage at start of treatment p < 0.0001, Breslow-Day test for homogeneity p = 0.790, logistic regression p < 0.0001.
c Study No. 609-06 (immunocompromised), Fisher's exact test.
d Study No. 609-06 (immunocompromised), chi-square test.
x: number of subjects with a non-ulcerative recurrence.
y: number of subjects starting treatment at the stage.

Effect on healing time and symptoms of herpes lesions.

Episode duration was shorter in the ME-609 Cream group than in the acyclovir and vehicle groups in all phase 3 studies, for all recurrences (i.e., ulcerative and non-ulcerative recurrences combined) and for ulcerative recurrences.

Mean Episode Duration (Days) in ME-609 Cream Phase 2 and Phase 3 Studies

Study No.	ME-609 Cream	Acyclovir 5%	Vehicle	ME-609 Cream vs. Acyclovir 5% (p-value)	ME-609 Cream vs. Vehicle (p-value)
All Recurrences					
609-04 (Pivotal)	5.4	5.5	5.9	0.630	0.046
609-06 (Immunocompromised)	6.7	6.7	NA	NA	NA
Ulcerative Recurrences					
98-609-013 (Phase 2, UVR induced)[a]	5.2	NA	6.1	NA	0.084
609-04 (Pivotal)	5.7	5.9	6.5	0.365	0.008
609-06 (Immunocompromised)	6.6	6.9	NA	NA	NA
Non-Ulcerative Recurrences					
609-04 (Pivotal)	5.0	4.8	4.3	0.361	0.094
609-06 (Immunocompromised)	6.7	6.6	NA	NA	NA

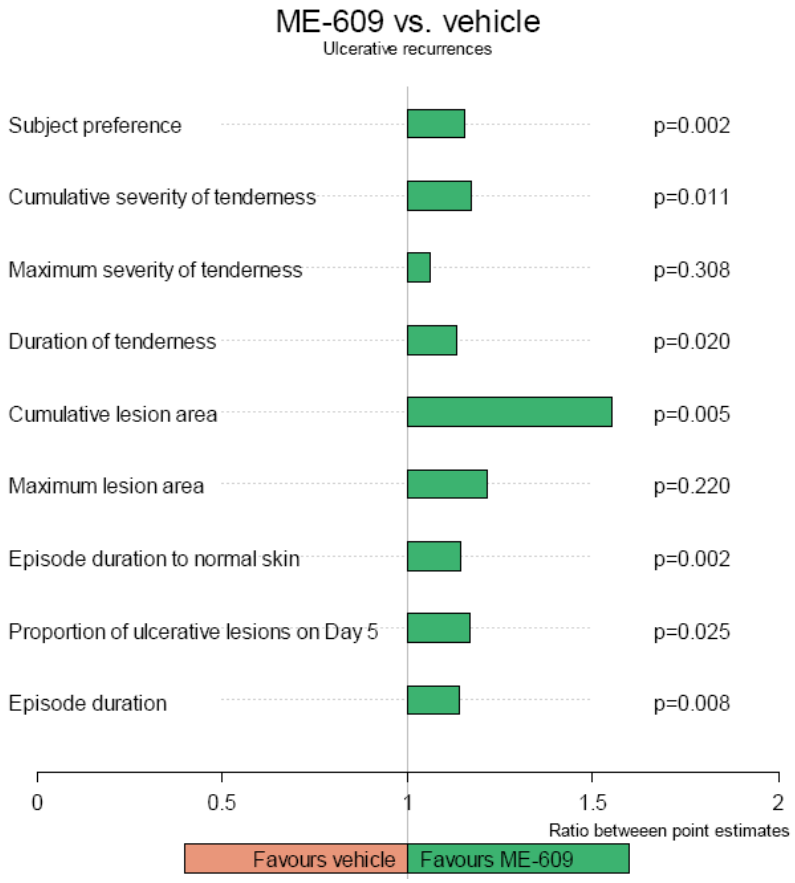
[a] Delayed classical lesions. NA – not applicable

Among subjects who experienced ulcerative lesions, a time-to-event analysis demonstrated that the median time to healing in the ME-609 Cream group was shorter (5 days) than in the vehicle group (6 days; p = 0.006) and comparable to the acyclovir group (5 days). On the last day of treatment (5 days after initiation), 40% of subjects in the ME-609 Cream group had healed the ulcerative stages of the recurrence, as compared to 34% in the acyclovir group and 29% on vehicle (not statistically tested). Looking at the time to full healing (to normal skin), the improvement in the ME-609 Cream group was even more pronounced; 1.5 and 1.4 days compared to vehicle in the pivotal trial and the phase 2 study, respectively [9.6 vs. 11.0 days; p = 0.002 and 9.0 vs. 10.4; p = 0.037.

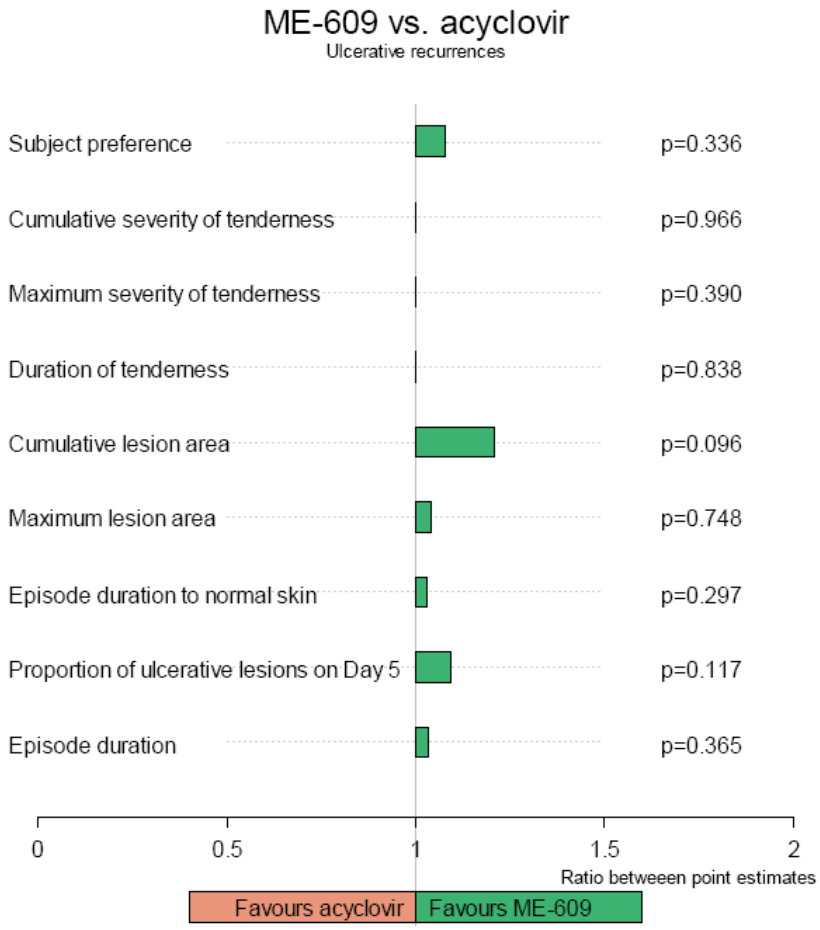
To illustrate the total clinical benefit of ME-609 Cream, an analysis of healing time for all recurrences (i.e., including both ulcerative and non-ulcerative recurrences) was performed. In this analysis, the impact of prevention was introduced by assigning zero values to non-ulcerative recurrences. The analysis demonstrated that the median time to healing in the ME-609 Cream group was significantly shorter than in the acyclovir group (3 vs. 4 days, p = 0.0295) and in the vehicle group (3 vs. 5 days; p < 0.0001).

Other lesion related parameters were improved to a similar extent by ME-609 Cream treatment. In the comparison with vehicle, these improvements were in most cases of clinically relevant size and statistically significant, whereas the improvements compared with acyclovir in the ME-609 vehicle were consistent across most parameters, but smaller and most often not statistically significant. The mean maximum lesion area was reduced by ME-609 Cream from 56 to 41 mm^2 in UVR-induced lesions and from 50 to 41 mm^2 in the pivotal trial compared to vehicle, corresponding to a reduction by 27% and 17% (both non-significant). The mean maximum lesion area in the ME-609 Cream group was comparable to that in the acyclovir group in the pivotal trial and larger than in the acyclovir group in immunocompromised subjects (acyclovir: 24 mm^2 vs. ME-609 Cream (37 mm^2). This latter difference was largely driven by a few outliers, as evidenced by median values of 22 and 20 mm^2, respectively.

Effect of ME-609 Cream Compared to Vehicle in Subjects with Ulcerative Lesions



Effect of ME-609 Cream Compared to Acyclovir in Subjects with Ulcerative Lesions



In the pivotal study, the primary efficacy endpoint was also analysed for different subgroups according to age, gender, stage of start of the treatment, number of episodes per year, years with disease and compliance. These subgroup analyses showed a consistent pattern between different subgroups regarding the efficacy results, with an order of magnitude of efficacy ME-609 > acyclovir > placebo.

Clinical safety

ME-609 Cream represents a novel approach to the treatment of recurrent HSV infection in which acyclovir and hydrocortisone control the viral replication and the inflammation, respectively. Both of the active components of ME-609 Cream, acyclovir and hydrocortisone, are already approved for clinical use in topical products at the dosages used in ME-609 Cream, both are well tolerated and the safety profiles of these ingredients are well established. However, the addition of hydrocortisone to an infectious lesion may be anticipated to prolong healing due to the immunomodulative effect and to have a potential to promote secondary infections. These aspects must be carefully addressed before the combination can be considered for approval.

The safety of ME-609 Cream has been assessed in 9 studies; 5 skin blanching/dermal/photosafety studies, one phase 2 study and three phase 3 studies.

Summary of Exposure (All Studies)

Study No.	Population	Study Type	Mean Duration of Exposure (Days)	ME-609 Cream	(ME-609 Vehicle	Acyclovir 5%[a]	Hydrocortisone 1%	ME-609B	Total Subjects
Number of Healthy Subjects Exposed									
99-609-005	Healthy	Phase 1, skin blanching	1 6	20 7	-	20 20	20 6	20 7	20 20
604598[b]	Healthy	Phase 1, skin irritation	4.2	36	36	36	-	-	36
604603	Healthy	Phase 1, skin sensitization	4.3+1	225	225	-	-	-	225
KGL6201	Healthy	Phase 1, phototoxicity	1	30	30	-	-	-	30
KGL6202	Healthy	Phase 1, photoallergy	6+1	50	50	-	-	-	50
		Total Healthy Subjects		**361**	**341**	**56**	**20**	**20**	**361**
Subjects with Recurrent Herpes Labialis Exposed									
98-609-013	Herpes labialis	Phase 2, (UV induced)	Not calculated	190	190	-	-	-	380
609-04	Herpes labialis	Phase 3, pivotal study	5.4	601	232	610	-	-	1443
609-06	Herpes labialis	Phase 3, immunocompromised	4.5	77	-	30	-	-	107
609-07	Herpes labialis	Phase 3, adolescents	5.6	134	-	-	-	-	134
		Total Subjects with Recurrent Herpes Labialis		**1002**	**422**	**640**	-	-	**2064**
Combined total of all healthy subjects and subjects with recurrent herpes labialis				**1363**	**763**	**696**	**20**	**20**	**2425**

a Zovirax® Cream was used in Study No. 99-609-005 (skin blanching) and Study No. 604598 (skin irritation), in the rest of the studies acyclovir (5%) in ME-609 vehicle was used.
b In Study No. 604598, 36 subjects also received both a positive (SDS) and a negative control (NaCl)

Phase 1 studies

Based on the results from the five dermal and photosafety studies, ME-609 Cream and the ME-609 vehicle were demonstrated to cause skin irritation which was similar in nature and frequency to that with Zovirax® Cream. Contact sensitization may occur with ME-609 Cream or the ME-609 vehicle and, where sensitivity tests have been conducted, the reactive substance has been shown to be an excipient (propylene glycol) or hydrocortisone. No phototoxicity or photocontact allergenicity was detected with ME-609 Cream or the ME-609 vehicle. Based on the present results, the potential for skin irritation can be predicted to be similar for ME-609 Cream and Zovirax® Cream.

Phase 2 and Phase 3 studies

A total of 2,064 subjects with recurrent herpes labialis (RHL) were enrolled in the Phase 2 and 3 studies. At least one dose of ME-609 Cream was applied in 1,002 of these subjects, of which 791 were immunocompetent adults, 134 were adolescents and 77 were HIV-infected immune-compromised subjects (mean CD4+ T-cell count, 326/mm^3). Adverse events were reported more commonly in the phase 2 study in which HSV recurrences were induced using ultraviolet radiation than in the phase 3 studies where the recurrences were not induced.

Adverse Events: Safety Dataset Phase 2 and Phase 3 Studies

Study No.	98-609-013		609-04			609-06		609-07	Phase 3 Totals		
Treatment	ME-609 N = 190	ME-609 Vehicle N = 190	ME-609 N = 601	Acyclovir, 5% N = 610	ME-609 Vehicle N = 232	ME-609 N = 77	Acyclovir, 5% N = 30	ME-609 N=134	ME-609 N=812	Acyclovir, 5% N=640	ME-609 Vehicle N=232
Subjects with At Least 1 AE [n (%)]	123 (64.7%)	126 (66.3%)	111 (18.5%)	100 (16.4%)	45 (19.4%)	6 (7.8%)	5 (16.7%)	5 (3.7%)	122 (15.0%)	105 (16.4%)	45 (19.4%)
Total AEs (n)	455	584	152	139	64	6	5	5	163	144	64
Subjects with Severe AEs [n (%)]	16 (8.4%)	24 (12.6%)	7 (1.2%)	1 (0.2%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.9%)	1 (0.2%)	3 (1.3%)
Subjects with Treatment-Related AEs [n (%)]	70 (36.8%)	75 (39.5%)	32 (5.3%)	21 (3.4%)	14 (6.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	34 (4.2%)	21 (3.3%)	14 (6.0%)
Subjects with AEs Leading to Discontinuation of the Study Drug [n (%)]	0 (0.0%)	3 (1.6%)	2 (0.3%)	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	3 (0.3%)	1 (0.2%)	1 (0.4%)
Subjects with SAEs [n (%)]	0 (0.0%)	0 (0.0%)	2 (0.3%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	2 (0.2%)	2 (0.3%)	0 (0.0%)
Deaths [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

In the combined Phase 3 studies, “other herpes labialis recurrences”, headache, nasopharyngitis, upper respiratory tract infection and dry lip were the only events reported in ≥ 1% subjects in any treatment group and all occurred in a higher percentage of subjects in the ME-609 vehicle group than in the ME-609 Cream group

Local Application Site Adverse Events

Local application site reactions have been examined in detail due to the topical route of administration of ME-609 Cream and because these events account for the majority of labeled undesirable effects of the marketed formulations of the individual active ingredients, where the excipients account, at least in part for some of the effects seen. In the Phase 2 study, all but one local application site AE (dry skin) occurred at a similar frequency between groups or at a lower frequency in the ME-609 Cream group than the vehicle group. In the Phase 3 studies the frequency of local application site AEs was similar in the ME-609 Cream, acyclovir in ME-609 vehicle and ME-609 vehicle groups. All but three of these events (one case each of swelling of the upper lip, application site irritation and application site dryness) were mild or moderate in severity.

Adverse events considered by investigators to be possibly or probably related to study treatment:

In the Phase 2 study, a higher proportion of subjects reported adverse events considered by investigators to be possibly or probably related to study treatment in the vehicle group (39.5%) than in the ME-609 Cream group (36.8%). The most frequent preferred terms were: skin dry, pain, edema mouth, skin reaction localized and headache.

Treatment-Related Adverse Events; PTs by Treatment Group in Pooled Phase 3 Studies.

Study No.	609-04			609-06		609-07	Phase 3 Totals		
Treatment	ME-609	Acyclovir, 5%	ME-609 Vehicle	ME-609	Acyclovir, 5%	ME-609	ME-609	Acyclovir, 5%	ME-609 Vehicle
WHO Preferred Term	N = 601	N = 610	N = 232	N = 77	N = 30	N=134	N=812	N=640	N=232
Subjects with At Least 1 Treatment-Related AE [n (%)]	**32 (5.3%)**	**21 (3.4%)**	**14 (6.0%)**	**1 (1.3%)**	**0**	**1 (0.7%)**	**32 (3.9%)**	**21 (3.3%)**	**14 (6.0%)**
Other Herpes Labialis Recurrences[a] [n (%)]	5 (0.8%)	3 (0.5%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.6%)	3 (0.5%)	3 (1.3%)
Upper Respiratory Tract Infection [n (%)]	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Lip Dry [n (%)]	7 (1.2%)	2 (0.3%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.9%)	2 (0.3%)	3 (1.3%)
Chapped Lips [n (%)]	1 (0.2%)	3 (0.5%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.5%)	1 (0.4%)
Nausea [n (%)]	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Cheilitis [n (%)]	3 (0.5%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	1 (0.4%)
Vomiting [n (%)]	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hypoaesthesia Oral [n (%)]	0 (0.0%)	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.4%)
Lip Disorder [n (%)]	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Oral Discomfort [n (%)]	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Paraesthesia Oral [n (%)]	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Application Site Dryness [n (%)]	3 (0.5%)	3 (0.5%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	3 (0.5%)	3 (1.3%)
Application Site Irritation [n (%)]	4 (0.7%)	4 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.5%)	4 (0.6%)	0 (0.0%)
Application Site Erythema [n (%)]	1 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.3%)	0 (0.0%)
Application Site Anaesthesia [n (%)]	0 (0.0%)	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.4%)
Application Site Paraesthesia [n (%)]	2 (0.3%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.2%)	0 (0.0%)
Application Site Exfoliation [n (%)]	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Application Site Pain [n (%)]	0 (0.0%)	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.4%)
Application Site Hypersensitivity [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Application Site Inflammation [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Fatigue [n (%)]	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Headache [n (%)]	2 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.4%)
Dysgeusia [n (%)]	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
Swelling Face[b] [n (%)]	1 (0.2%)	0 (0.0%)	1 (0.4%	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.4%)
Skin Exfoliation [n (%)]	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Vertigo	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

a Other herpes labialis recurrences, although a natural part of the disease, were documented as AEs and coded as "herpes simplex" in Study No. 609-04 (pivotal) and Study No. 609-07 (adolescents) to enable proper monitoring of frequency. In Study No. 609-06 (immunocompromised), other herpes recurrences were not coded as AEs so were not assessed for treatment relation.
b Reported term/verbatim used "swelling upper lip". Mapped as PT "swelling face".

Severe Adverse Events:

In the pooled phase 3 studies, the proportions of subjects with at least one severe AE were: 7/812 subjects (0.9%) in the ME-609 group, 1/640 subject (0.2%) in the acyclovir in ME-609 vehicle group and 3/232 subjects (1.3%) in the ME-609 vehicle group. The only severe AE that occurred more than once was "herpes simplex" designating other herpes labialis recurrences. Two subjects (0.2%) in the ME-609 group and one subject (0.4%) in the ME-609

vehicle group had severe other herpes labialis recurrences. Two subjects in the ME-609 group and one subject in the ME-609 vehicle group had severe AEs that were also topical treatment AEs (swelling face [limited to upper lip], application site irritation, application site dryness).

Serious adverse events and deaths:
There were four serious adverse events (SAEs): three SAEs occurred in the pivotal study and one SAE occurred in Study 609-06 (immunocompromised). SAEs were experienced by two subjects treated with ME-609 (both chest pain of moderate severity) and two subjects treated with acyclovir in ME-609 vehicle (both pneumonia of moderate severity). All these four subjects continued study medication and completed the study. No SAE was considered by the investigator to be related to study medication. No SAE was a topical treatment AE. There were no deaths in any of the studies.

Special monitoring:
Other herpes recurrences (HSV lesions that appeared > 72 hours after the first recurrence and were > 10 mm from the study recurrence) were reported by 4.9%, 6.9% and 7.3% of subjects in the ME-609, acyclovir and placebo groups, respectively. Thus there was no indication that the addition of hydrocortisone increased the frequency of secondary HSV recurrences.

Data concerning viral shedding and acyclovir resistance was monitored in all comparative studies. In the pivotal study, the frequency of virus-positive lesions was comparable between ME-609 and acyclovir, and lower than in the placebo group. HSV was isolated in 22% (32/143), 24% (44/182) and 40% (32/143) samples in the ME-609, acyclovir and placebo groups, respectively. Thus, the addition of hydrocortisone did not seem to enhance viral replication as compared to acyclovir alone in healthy adults. No acyclovir resistant samples were identified, as analysed by genotypic and phenotypic methods. Similar findings were made in study ME-609-06 (immunosuppressed), where PCR-positive samples were obtained from 29% and 27% of subjects in the ME-609 and acyclovir groups, respectively. None of the subjects had reduced acyclovir sensitivity due to a mutation in the TK or DNA polymerase genes or as identified in the plaque reduction assay.

Safety in special populations:
Adolescents: Five adverse events were reported among the 134 (3.7%) adolescents in Study No. 609-07; two subjects with “other herpes recurrences” and one subject each with rhinitis, asthma and application site inflammation. All events were mild or moderate in intensity. Only the application site inflammation, which resulted in treatment being discontinued, was considered by the investigator to be related to study drug (ME-609 Cream). No other local adverse events were recorded, which is in contrast to the pivotal study [Study No. 609-04 (pivotal)] where local site application AEs were reported in 5.0% of subjects.

Immunocompromised patients: In this study in HIV-infected immunocompromised subjects (mean CD4+ T-cell count, 326/mm^3), adverse events were reported for 6 (8%) of ME-609 Cream subjects and for 5 (17%) of acyclovir subjects. All adverse events were of mild or moderate intensity. Application site hypersensitivity was reported for 1 (1%) ME-609 Cream subject and was the only event considered by the Investigator to be probably related to study medication. All other adverse events were infections, consistent with the immunocompromised status of the study population, and considered unrelated to study medication. No subjects were withdrawn from the study due to adverse events. Thus, the addition of hydrocortisone to acyclovir in ME-609 Cream in immunocompromised patients did not seem to significantly change lesion severity, lesion healing time or the frequency of adverse events compared to acyclovir alone and no signs of local super-infections were observed with the combination.

Discontinuation due to adverse events:
A total of 8 subjects prematurely discontinued study treatment due to AE. Of these were 3 treated with ME-609, one with acyclovir in vehicle and 4 with ME-609 vehicle. All AEs leading to treatment discontinuation were topical treatment AEs related to study treatment except one AE of headache in a ME-609 vehicle-treated patient, which was not topical or related to study treatment. Only one of the topical treatment AEs leading to study drug discontinuation was considered as severe (swelling of upper lip).

Risk Management Plan

MAH has submitted a Risk Management Plan.
There are no new safety concerns identified with this combination product.
The identified risks in the Risk Management Plan are local skin reactions and contact dermatitis.

Specific Risk minimisation programmes for Xerclear are not proposed.
Routine risk minimisation activities are planned for Xerclear

IV.1 Discussion on the clinical aspects

Efficacy was demonstrated for Xerclear versus placebo for reduction of both progression of cold sore episodes to ulcerative cold lesions and of the episode duration in immunocompetent adults and adolescents with early signs and symptoms of recurrent herpes labialis, of which the former endpoint has not previously been achieved for topical acyclovir. The submitted data also support superiority over acyclovir as a single agent in this respect. Thus, this specific effect of Xerclear is probably attributed to the addition of hydrocortisone to this combined product. The protective effect was most evident when treatment was initiated in the prodromal stage, but the effect was maintained also in subjects initiating therapy in the erythema or papular stage. Safety data from the clinical studies in approximately 1000 subjects with recurrent herpes labialis infections indicate that the nature and frequency of all AEs and local application site adverse events reported in the Xerclear groups were generally mild to moderate in nature and similar to those in the acyclovir and placebo groups, and seem to be comparable to those associated with Zovirax® Cream. However, the number of patients studied is relatively low and a direct comparison between Xerclear and the reference product, Zovirax® Cream is lacking.

Considering the limited treatment benefit of currently approved topical antiviral agents for recurrent herpes labialis and the vast clinical experience of the two active substances, acyclovir and hydrocortisone, the added benefit, although still modest, for the target patients in terms of prevention of development of ulcerative lesions exerted by this combination product can be considered as a contribution to the available therapy arsenal.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Xerclear, 50 mg/g + 10 mg/g cream, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Xerclear, 50 mg/g + 10 mg/g cream was successfully finalised on 2009/10/14.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se