CBG MEB

Public Assessment Report

Scientific discussion

Herpirax 50 mg/g, cutaneous stick

(aciclovir)

NL/H/3877/001/MR

Date: 14 February 2018

This module reflects the scientific discussion for the approval of Herpirax 50 mg/g, cutaneous stick. The procedure was finalised on 14 November 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BHT	Butylhydroxytoluene
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Herpirax 50 mg/g, cutaneous stick from Stasisport Pharma N.V.

The product is indicated for the treatment of cold sores caused by the herpes simplex virus (recurrent herpes labialis).

A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns a hybrid application, with a change in pharmaceutical form (cutaneous stick) compared to the reference product (cream). The reference product is Zovirax 5% cream, registered in Italy by GlaxoSmithKline SpA since 1984. The reference product authorised in the Netherlands is Zovirax Koortslip 50 mg/g cream (NL License RVG 19078). It has been registered by GlaxoSmithKline Consumer Healthcare B.V. since 1996.

The concerned member states (CMS) involved in this procedure were Belgium and Portugal.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Herpirax 50 mg/g cutaneous stick is a cylindrical, white to light yellow mass, which is slightly perfumed. The product is packaged in a polystyrene stick with an acetalyc resin cursor closed with a cap. The stick is enclosed in a cardboard box together with the leaflet.

The excipients are: castor oil, semi-synthetic glycerides (hard fat), carnauba wax, beeswax (white), octyldodecanol, white paraffin, vanilla aroma, and butylhydroxytoluene.

II.2 Drug Substance

The active substance is aciclovir, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white crystalline powder, which is slightly soluble in water, freely soluble in dimethyl sulfoxide and very slightly soluble in ethanol. It dissolves in dilute solutions of mineral acids or alkali hydroxides. No evidence is present of different polymorphic forms. Aciclovir does not have a chiral centre and therefore it has no stereo- or enantioisomers.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP with some additional requirements obtained from the USP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two pilot-scale batches. This is acceptable since a CEP is available.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients and their functions explained. It is likely that butylhydroxytoluene (BHT) protects the product from degradation caused by auto-oxidation of the fat basis of the stick. The concentration of 0.02% BHT has been adequately justified as the lowest effective concentration. During development the composition and process parameters were optimised until the final formulation was obtained. No bioequivalence study has been performed since this could not be demonstrated for this locally applied, locally acting product. A non-inferiority study was conducted and is described in section IV 'Clinical aspects'. Overall, the pharmaceutical development has been sufficiently described.

Manufacturing process
The manufacturing process consists of melting/pouring, stirring, dispersing, cooling, and filling. The process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for five pilot-scale batches. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable. For white paraffin the nominal value of the drop point has been laid down. For vanilla aroma additional information has been provided by the supplier. All excipients are adequately controlled.

Quality control of drug product
The product release specification includes tests for appearance, identification (aciclovir and BHT), assay (aciclovir and BHT), related substances, drop point, and average weight. The end-of-shelf-life specification is identical to the release specification. An additional specification has been included for content uniformity. Data have been submitted demonstrating the stability indicating nature of the HPLC method used for impurity testing. The analytical methods have further been adequately described and validated.
Batch analytical data from the proposed production have been provided on five pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for six pilot-scale batches of which four were stored at 25°C/60% RH (18 and 36 months) and at 40°C/75% RH (6 months). The other two batches are stored at 30°C/65% RH (36 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a polystyrene stick with an acetalyc resin cursor and polystyrene cap. Stability data showed no up or downward trends, the results remained relatively stable for all parameters tested. For the batches stored at intermediate condition, related substances were first tested after 36 months only and showed some out-of-specification results. However, as impurities stayed well within specification after 6 months storage at 40°C/75%RH, the product does not need to state a maximum storage temperature. A shelf-life of 3 years can be granted when stored in the original packaging in order to protect from light. An in-use stability of 1 month below 25°C has been justified based on an in-use study simulating use.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Herpirax 50 mg/g has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Herpirax is intended for substitution of existing products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Zovirax 50 mg/g cream, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Aciclovir is a well-known active substance with established efficacy and tolerability.
This application was made on the basis of Article 10.3 of Directive 2001/83/EC. As Herpirax 50 mg/g cutaneous stick is a topical preparation, bioequivalence cannot be demonstrated through bioavailability studies. Since this hybrid application concerns a different pharmaceutical form compared to the reference product Zovirax cream, clinical studies are required to demonstrate non-inferiority. No additional pharmacological, toxicological studies or full clinical trial program has been conducted or submitted as part of this application. A clinical overview based on literature has been provided.

With the new pharmaceutical form, a cutaneous stick, the patient does not need to touch the product with his fingertips, which theoretically reduces the chance of virus transmission through fingertips.

For this application the following guidances are applicable: the Note for Guidance on the clinical requirements of locally applied, locally acting products containing known constituents (CPMP/EWP/239/95 final), on choice of control group in clinical trials (CPMP/ICH/364/96) and on statistical principles for clinical trials (CPMP/ICH/363/96), the guideline on the choice of non-inferiority margin (EMEA/CPMP/EWP/2158/99) and the point to consider on switching between superiority and non-inferiority (CPMP/EWP/482/91).

To support the application the MAH submitted the following clinical studies:
- Study AC/DIP/2007: a two-armed non-inferiority study to compare Herpirax 50 mg/g lipstick to Zovirax 5% cream.
- Study 4PH/2011/002: a double-blind placebo controlled study.

The studies are briefly discussed below.

IV.1 Clinical efficacy

IV.1.1 Study AC/DIP/2007 - Efficacy and tolerability of Herpirax 50 mg/g versus Zovirax 5% cream

Design
This study was an open-label, monocentric, multiple dose, non-inferiority study in 128 adults to evaluate the efficacy of Herpirax 5% lipstick and the safety of both the test and the reference product.
Adult patients with a clinical diagnosis of active infection from herpes labialis in prodromal phase were assigned to receive either Herpirax 5% Lipstick or Zovirax 5% cream. Participants were males and females, aged 18 to 70 years, of Caucasian origin, who had normal physical examination, ECG and laboratory evaluations. Female participants had a negative result for pregnancy test.

The lipstick or reference product was applied 5 times daily on the lesion per application (at 7:00, 11:00, 15:00, 19:00 and 23:00) for no more than 7 consecutive days, until healing i.e. formation of a hard crust. The lipstick was administered 5 times on each time point (equalling 120 mg), which is in accordance with the posology. The study ended at the post-study visit, one day after the formation of a hard crust.

The primary objective was to evaluate the efficacy of the test formulation in comparison to the reference one. Non-inferiority with regard to mean healing time (days) was hypothesised, with a margin of ±1 day, based on the results of 4 clinical trials using the same efficacy measure.
The secondary objective was to evaluate the general safety of both test and reference formulation.

Justification of sample size and non-inferiority margin was based on previous, placebo-controlled studies on the efficacy of aciclovir. The MEB noted that the preferred study design to demonstrate non-inferiority of Herpirax lipstick would have been a three-armed trial. The submitted study, however, lacks a placebo-arm and therefore internal validation of assay sensitivity.

Efficacy evaluation
Primary endpoint
Healing time, i.e. the requested time (days) for formation of a hard crust from start of treatment. The healing time was monitored by filling in of a Daily Diary by patient and a daily morning phone call to the patients by a Clinical Investigator.

Secondary endpoint
Patient-assessed severity of pain (VAS scale 0-100 mm), performed on study day 1 (the day after the screening day) and on the last treatment day by the Clinical Investigator.
Lesion size (small, medium, large, very large) evaluation, performed on study day 1 and on the last treatment day by the Clinical Investigator.
Maximum lesion extension (mm) evaluation, performed on study day 1 and on the last treatment day by the Clinical Investigator.
Burning was daily assessed and recorded by the patient in the Daily Diary on a ordinal (0=absent burning to 3=intense burning) scale.
Itching was daily assessed and recorded by the patient in the Daily Diary on a ordinal (0=absent itching to 3=intense itching) scale.

Safety Evaluation
Participants were evaluated for laboratory test results at pre- and post-study visit, vital signs recorded during pre- and post-study visit and adverse events during the whole study period.

Participant flow/Recruitment
A total of 128 participants were screened and 128 were enrolled and randomized. Out of 128 participants, 64 received the test treatment and 64 received the reference treatment. All participants enrolled satisfied the inclusion/exclusion criteria as specified in the study protocol and all participants completed the study. The analysis was performed based on all subjects.

Conduct of the study
No major protocol violations were reported. Minor protocol violations included *wrong administration time* (within ±3 hours from the administration times specified in the protocol; n=28) and concomitant therapies/medication not related to the pathology (n=12).

Baseline data
The majority of participants was female (n=91; 71.1%). The mean age was approximately 35 years (range 17 – 64). Demographic data were not reported separately for the different treatment groups. Treatment groups did not differ on severity of pain, lesion size, lesion extension, burning or itching at study entry.

Statistical methods
The analyses were based on the intention to treat (ITT) population, which in this study was equal to the per protocol (PP) population.
The primary analysis was intended to demonstrate non-inferiority (margin 1.0 day) of Herpirax 5% lipstick compared to Zovirax 5% cream. The difference in healing time (days) was assessed by constructing a 95% confidence interval around the difference between the healing time values obtained in both treatment arms. A time-to-event analysis ("survival analysis") was also performed (Kaplan-Meier method), taking as the event the formation of hard crust.
The treatment groups were furthermore compared to assess their homogeneity at baseline. The effect of each treatment was assessed with respect to the baseline values obtained at study entry.
Parametric data were analysed using Student's *t* test for continuous variables. Nonparametric data were analysed using the Mann-Whitney U test for group differences. All statistical evaluations were two sided and $P < 0.05$ was considered significant. Regarding safety, only descriptive data were provided, no statistical testing was performed.

Efficacy results
Primary endpoint
The mean healing time was 4.67 days for Herpirax 5% lipstick and 4.81 days for Zovirax 5% cream. This represented a mean difference of -0.14 days (95% CI: -0.55, 0.27) in favor of Herpirax 5% lipstick. Criteria for non-inferiority of Herpirax 5% lipstick were met. According to the Kaplan-Meier survival test, the 2 treatments did not differ with regard to time to healing.

Secondary endpoints:
Herpirax 5% lipstick did not differ from Zovirax 5% cream with regard to pain (mean difference -.06; 95% CI: -1.73, 1.62), lesion extension (mean difference 0.51; 95% CI: -0.24, 1.25), lesion size (median=0; interquartile range=0; z=-1.429; p=.153) , burning (median=0; interquartile range=0; z=-.429; p=.668) and itching (median=0; interquartile range=0; z=-1.353; p=.176).

For both treatments, there were significant reductions from baseline values for all variables.

Safety results
The extent of exposure to both the test and reference products was no more than seven consecutive days with a dose of 600 mg/day of aciclovir per participant. No adverse events were reported during the study.

Lack of placebo control
Non-inferiority of Herpirax 5% lipstick compared to Zovirax 5% cream was demonstrated as the 95% CI around the mean difference between both products entirely lies within the established non-inferiority margin. However, based on the 2-arm active comparator study, no conclusions can be drawn with regard to the efficacy compared to placebo. For this kind of products the efficacy compared to placebo and active component should be evaluated in order to draw final conclusions, in line with the applicable Notes for Guidance (CPMP/EWP/239/95 final and CPMP/ICH/364/96). Therefore, the efficacy compared to placebo should also be evaluated in order to draw final conclusions, and the MAH submitted a second study.

IV.1.2 Study 4PH/2011/002 - Efficacy and safety of Herpirax 50 mg/g versus placebo

Design
This study was a randomised, double-blind, placebo controlled, parallel group study in males and females, aged 18 to 70 years, of Caucasian origin, who had a clinical diagnosis of active infection from herpes labialis in prodromal phase and normal physical examination, ECG and laboratory evaluations. Female participants had a negative result for pregnancy test.

The patients were assigned to receive either Herpirax 5% lipstick or placebo lipstick. The excipients in the test product and placebo are the same.

The lipstick was applied 5 times (equalling 120 mg) on the lesion per application. Five daily administrations were scheduled every four hours from the first administration (in study day 1) until healing, i.e. complete re-epithelialization of lesions, for no more than seven consecutive days.

The primary objective was to evaluate the efficacy of the test formulation in comparison to placebo.
The secondary objective was to evaluate the general safety of the test formulation and placebo.

Efficacy evaluation
Primary endpoint
Healing time, i.e. the number of days from the beginning of the therapy until the complete re-epithelialization of lesions.

Secondary endpoint
- Reduction in patients assessed severity of pain (using a Visual Analogue Scale: 0-100 mm);
- Reduction in lesion size (small, medium, large, very large);
- Reduction in lesion extension (mm);
- Reduction of burning and itching (absent, slight, medium and intense).

Safety Evaluation
During the whole study period physical examination, vital signs, resting 12-lead ECG pre and post study and adverse events were evaluated..

Participant flow / Recruitment
Seventy (70) subjects have been screened, seventy (70) enrolled, seventy (70) have been treated and sixty-nine (69) finished that study according to the protocol. One patient dropped out due to adverse events.

Conduct of the study
No major protocol violations were reported. Minor protocol violations included missing of treatment compliance measurement because of failed return of the assigned treatment by patient (n=18) and concomitant therapies/medication not related to the pathology (n=5).

Baseline data
The majority of participants was female (n=42; 60%). The mean age was approximately 27 years.
There were no significant differences between the test and placebo groups at study entry, with regard to pain, extension, burning and itching.

Statistical methods
The statistical analyses have been performed according to the “Intention To Treat” (ITT) and “Per Protocol” (PP) analysis principles. All randomised patients have been included in the Intention-to-Treat population. Only patients showing no/minor protocol deviations have been included in the Per-Protocol population.
The results of the two treatment groups have been compared using parametric and nonparametric tests coherently with the type of data. In particular, the difference between the mean of the necessary days from the beginning of therapy until complete re-epithelialisation (healing time) of the test product and the mean of the healing time of the placebo have been compared using Student’s t test.
For subjects whose duration of episode is unknown, a duration of 15.0 days have been assigned. Student’s t test was used to assess the difference in maximum lesion area and pain score. Other secondary efficacy variables were analysed using chi-square test.

According to CPMP/ICH/363/96 and CPMP/EWP/482/99, both two-sided (at 95% significance level) and one-sided tests (at 97.5% significance level) have been performed and the superiority of the test formulation over the placebo was assessed by constructing a two-sided 95% Confidence Interval around the difference between the mean of healing time of the test formulation and the mean of healing time of the placebo. Safety variables have been fully described.

Efficacy results
Primary endpoint
The mean healing time in the ITT analysis was 4.94 days for Herpirax 5% lipstick and 7.80 days for placebo (difference 2,86; 95% confidence interval of the difference was 1,554 – 4,160). For the PP analysis only one patient in the placebo group was left out. As expected the results for the PP analysis were in line with the ITT results: mean healing time 4.94 days for Herpirax 5% lipstick and 7.59 days for placebo, (difference 2,65; 95% CI of the difference 1.394 -3.897).

A difference of 1.1 day was considered a clinical mean full difference. The 95% confidence interval of the difference was 1,554 – 4,160. The 95% confidence interval of the difference of healing time between the two treatments was entirely above 1.1, demonstrating that the test treatment is superior to the placebo.

Secondary endpoints
There were significant differences between the two groups at the final visit for pain (VAS mean placebo 5,00 versus aciclovir 5% 0,43 p<0,05 Student's t test; and extension mean placebo 1,23 versus aciclovir 5% 0 p<0,05 Student's t test.
The categorical variables, size, burning and itching, were too sparse at the final visit to be analyzed correctly.

Safety results
Of the total 70 patients 35 were exposed to the aciclovir stick 5% and 35 were exposed to the placebo formulation. Four adverse events occurred, all in the placebo group, none was considered related to the study drug.

IV.1.3 Conclusion on clinical study AC/DIP/2007 and 4PH/2011/002

Non-inferiority compared to Zovirax was shown in the first submitted active controlled study. Although the predefined non-inferiority margin of 1 day was considered to be too large the results were within a more acceptable margin of 0.5 day or even 0.33 day.

Superiority over placebo was shown in the second submitted placebo controlled study.

The definition of the primary endpoint was different in both studies. It was crust forming in the active controlled study, while it was complete re-epithelialization in the placebo controlled study.
In most studies complete re-epithelialization is used as primary endpoint. That was the reason for the applicant to choose complete re-epithelialization as primary endpoint in the second study. As both definitions are easy to diagnose for the patient himself as well as for the physician, both definitions can be considered acceptable. Because both studies are assessed as stand alone, it is no problem that a different primary endpoint was used.

The safety profile found was in line what is known for these products.

It was noted that the lipstick should be administered 5 times on each time point it is applied, while Zovirax cream has to be applied only once each time it is used. There is a risk that patients might use too little of the lipsticks i.e. not applying the lipstick 5 times each time it should be applied. However, the instructions in the SmPC and package leaflet are clear and it is the responsibility of the patient to use the product as mentioned in the product information.

IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Herpirax.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity reactions Decreased virus sensitivity with prolonged or repeated courses of aciclovir in severely immune compromised patients
Important potential risk	Use on mucosal tissues such as mouth, genitalia and eye
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zovirax. The MAH demonstrated through a non-inferiority study that the efficacy and tolerability are comparable to the innovator. Furthermore, a placebo controlled study was conducted to demonstrate superiority over placebo. Risk management is adequately addressed. In conclusion, this hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results of the test on the PL showed that some aspects can be improved. In line with the results of the readability test italic style was replaced by regular style across the leaflet. Also in section 4 the layout was adapted. The comments raised in the user test have been adequately addressed. The package leaflet meets the relevant requirements.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Herpirax 50 mg/g, cutaneous stick has a proven chemical-pharmaceutical quality and is a hybrid form of Zovirax 50 mg/g cream. Zovirax is a well-known medicinal product with an established favourable efficacy and safety profile.

Herpirax has been shown to be non-inferior to Zovirax cream, and superior over placebo.

The Board followed the advice of the assessors. Herpirax 50 mg/g, cutaneous stick was authorised in the Netherlands on 26 March 2014.

There was no discussion in the CMD(h) during the mutual recognition procedure. Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. The MRP was finalised with a positive outcome on 14 November 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse