# CLINICAL REVIEW

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| **Date** | November 15, 2013 |
| **From** | Kirk Chan-Tack, M.D. – Clinical Reviewer<br>Division of Antiviral Products (DAVP) |
| **Subject** | Clinical Review |
| **NDA#/Supplement#** | 22-436/SN0060 |
| **Applicant** | Valeant |
| **Date of Submission** | July 31, 2013 |
| **PDUFA Goal Date** | January 31, 2014 |
| **Proprietary Name / Established (USAN) names** | Xerese (5% acyclovir and 1% hydrocortisone) topical cream |
| **Dosage forms / Strength** | 5% acyclovir and 1% hydrocortisone topical cream |
| **Proposed Indication(s)** | Early treatment of signs and symptoms of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores in children ages 6-11 years |
| **Recommended:** | Approval |

## 1. Introduction

This clinical review summarizes the main issues for the Applicant's supplemental New Drug Application (sNDA). New safety data for children ages 6-11 years with signs and symptoms of recurrent herpes labialis (cold sores) were provided and included in proposed labeling. Overall, the safety profile of Xerese in children (ages 6-11 years) is similar to adults. Extrapolation of efficacy for Xerese in children ages 6-11 years is considered reasonable based on the available data since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in children compared to adults and adolescents.

## 2. Background

In July 2009, Xerese (5% acyclovir and 1% hydrocortisone) topical cream was approved for early treatment of signs and symptoms of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores in adults and adolescents 12 years of age and older. This approval was based on the results from three phase 3 trials (Study 609-04, 609-06, and 609-07) summarized in the following table.

**Table 1: Phase 3 Clinical Trials**

| Study | Study Type | Country or Continent | Design | Dose and Duration | Total No. of Subjects/ |
|---|---|---|---|---|---|
| 609-04 (Adults ≥18 years old) | Pivotal safety and efficacy | United States, Canada | Multi-center, randomized, double-blind, active and vehicle-controlled, three arm, subject initiated study | 5 times per day for 5 days | 1443 treated and evaluable subjects: ME-609 (n=601); 5% acyclovir in ME-609 vehicle (n=610); vehicle (n=232) |
| 609-06 (HIV+ adults ≥18 years old) | Safety | Russia, Ukraine | Multi-center, randomized, double-blind, active-controlled, subject | 5 times per day for 5 days | 107 treated and evaluable subjects: ME-609 (n=77); 5% acyclovir in ME-609 |

| Study | Study Type | Country or Continent | Design | Dose and Duration | Total No. of Subjects/ |
|---|---|---|---|---|---|
| | | | initiated study | | vehicle (n=30); |
| 609-07 (Adolescents 12-17 years old) | Safety | Russia, Sweden | Open-label, multi-center, subject initiated safety study | 5 times per day for 5 days | 134 treated and evaluable subjects: ME-609 (n=134) |

Note: ME-609 (5% acyclovir and 1% hydrocortisone) was the name used during the development of Xerese.

Efficacy and safety data from Study 609-04 supported approval in adults. In Study 609-04, Xerese was superior to both placebo and acyclovir for reducing the incidence of ulcerative herpes lesions. Study 609-06 provided additional safety data in immunocompromised adults. Study 609-07 provided safety data to support approval in adolescents (ages 12-17 years). Extrapolation of efficacy for Xerese in adolescents was considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and adolescents.

Overall, Xerese is tolerable for the proposed treatment dose and duration (i.e. five times per day for five days). No new or unexpected toxicities were observed with Xerese compared to available safety data on its two approved principal constituents, 5% acyclovir cream and 1% hydrocortisone cream. Overall, the adverse event (AE) profile of Xerese in adolescents was similar to adults. Additionally, the AE profile of Xerese in a selected population of HIV-infected adults (from Study 609-06) was similar to immunocompetent adults (from Study 609-04).

In the three phase 3 trials described above, no deaths were reported and discontinuation rates were low. There was no evidence of an increase in discontinuation due to toxicity for Xerese compared to acyclovir or vehicle. Most AEs were mild. The most common adverse reactions (all grades, considered definitely, probably or possibly related to study treatment) were local skin reactions that occurred at the site of topical application. The adverse event profile was similar across trials.

During the End-of-Phase 2 meeting (July 6, 2005), DAVP agreed with the Applicant's proposed study outline to conduct a single-arm, multi-center, open-label, safety study in approximately 100 adolescents (ages 12-17 years). DAVP also stated that data in younger children (lower age limit to be determined) would be needed and would be required under the Pediatric Research Equity Act. In addition, DAVP informed the Applicant that data in younger children are also needed in support of a Written Request in order to obtain pediatric exclusivity.

A pre-NDA meeting with the Applicant was held May 22, 2008. An overview of efficacy and safety data from the phase 3 trials (Study 609-04, 609-06, and 609-07) was presented. The Applicant proposed to submit a request for deferral from studying ME-609 cream in patients 6 to 11 years of age, and a waiver from studying ME-609 cream in patients under 6 years of age, at the time of NDA submission. The Applicant proposed to conduct a single-arm, multi-center, open-label, safety study in approximately 50 children ages 6-11 years old. The proposed study would be conducted according to the same parameters used in the adolescent study (Study 609-07). A draft protocol synopsis for this pediatric study was provided in the Pre-NDA meeting briefing package. FDA comments stated that the Applicant's proposal was reasonable.

The Applicant's pediatric development plan was also discussed internally and with the Pediatric Review Committee (PeRC) as part of the review process for the original NDA submission:

- Due to the pathophysiology and epidemiology of the disease, DAVP and the PeRC agreed ME-609 is unlikely to be used in pediatric patients younger than 6 years old. Herpes labialis in children under 6 years of age is generally a primary infection, and not a recurrence.
- DAVP and the PeRC agreed that the pathophysiology of recurrent herpes labialis was sufficiently similar in adults and in pediatric populations ages 6 to 17 years.
- DAVP and the PeRC agreed that, in the pivotal phase 3 trial (Study 609-04, conducted in immunocompetent adults, ages 18 and older), ME-609 was superior to placebo for the prevention of ulcerative herpes lesions, and superior to acyclovir.
- DAVP and the PeRC agreed with the Applicant's proposal to extrapolate efficacy for Xerese in adolescents (ages 12-17 years) based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and adolescents. DAVP and the PeRC agreed that Study 609-07 provided sufficient safety data to support approval in adolescents.
- DAVP and the PeRC agreed to grant a partial pediatric waiver (for ages less than 6 years old), and also agreed that the Applicant should request a deferral for a pediatric study in children ages 6-11 years old.

The Applicant submitted the following timeline for the proposed single-arm, multi-center, open-label, safety study in children ages 6-11 years old (50 evaluable subjects) to be done as a required post-marketing study:

Deferred pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric subjects from 6 to 11 years of age:

| | |
|---|---|
| Protocol Submission Date: | November 2010 |
| Study Initiation Date: | November 2011 |
| Study Completion Date: | November 2012 |
| Final Study Report Submission Date: | May 2013 |

The proposed timeline and design for the study in children ages 6-11 years old was acceptable to DAVP and to the PeRC. If sufficient safety data are collected in children ages 6-11 years old and the safety profile in this pediatric population is shown to be similar compared to adults, DAVP and the PeRC considered that the Applicant's proposal to extrapolate efficacy for Xerese in children based on efficacy data from Study 609-04 would be reasonable.

As agreed, the Applicant conducted Study MP800, an open-label, multi-center, phase 3, subject/caregiver initiated safety study of Xerese in the treatment of recurrent herpes labialis in children 6 to 11 years of age. Study MP800 was designed to fulfill the above required pediatric study and the final study report was submitted to the NDA on April 23, 2013. However, at that time, the study report was not submitted as a formal supplement with proposed labeling to the NDA. The Applicant subsequently requested, and was granted a PREA deferral extension to

July 31, 2013 so the Applicant could submit the requested supplement with the pediatric assessment.

# 3. CMC/Device

The drug product used in the clinical trials submitted in the sNDA is identical to the product approved. No new CMC data were submitted in the sNDA.

# 4. Nonclinical Pharmacology/Toxicology

This sNDA contained no new preclinical pharmacology/toxicology data. Please refer to the original FDA review of the NDA for additional information.

# 5. Clinical Pharmacology/Biopharmaceutics

This sNDA contained no new pharmacokinetic (PK) data. Please refer to the original FDA review of the NDA for additional information.

# 6. Clinical Microbiology

This sNDA contained no new virology data. Please refer to the original FDA review of the NDA for additional information.

# 7. Clinical - Efficacy

The primary efficacy endpoint that was evaluated in Study 609-04 (in immunocompetent adults) was the proportion of subjects with non-ulcerative recurrences (i.e. proportion of subjects in whom the study recurrences does not progress beyond the papule stage), as assessed by study investigators. No primary efficacy endpoints were evaluated in Study MP800.

*Reviewer Comment*
In the original NDA submission, extrapolation of efficacy for Xerese in adolescents was considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and adolescents.

Study 609-04 was a multi-center, randomized, double-blind, active and vehicle-controlled, three arm trial to evaluate the safety and efficacy of Xerese cream versus acyclovir cream (in Xerese vehicle) and placebo (Xerese vehicle) for the treatment of recurrent herpes labialis in immunocompetent adults. This trial was of adequate design and sufficiently powered to study the safety and efficacy of Xerese at a dose of 5-times daily for 5 days in immunocompetent subjects with recurrent herpes labialis.

The primary endpoint was the proportion of subjects with non-ulcerative recurrences, defined as the proportion of patients in whom the study recurrences do not progress beyond the papule stage. The secondary endpoints were episode duration and duration to normal skin.

- Episode duration was defined as investigator assessment of time from treatment initiation to loss of hard crust for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.

- Episode duration to normal skin was defined as investigator assessment of time from treatment initiation to normal skin for an ulcerative lesion, and time from treatment initiation to no signs or symptoms for a non-ulcerative recurrence.

In Study 609-04, Xerese was superior to both placebo and acyclovir for reducing the incidence of ulcerative herpes lesions. Efficacy of Xerese in immunocompetent children was extrapolated based on the efficacy findings in immunocompetent adults (Study 609-04) and the overall similarities in the pathophysiology and clinical presentation in these patient populations.

### 7.1 Study design

Study MP800 was a single-arm, multi-center, open-label, phase 3 trial. All subjects received Xerese as their study medication. A total of 50 subjects were planned for treatment under this protocol.

**Study initiation date**: 21-Feb-2012 (first patient enrolled)
**Early termination date**: Not applicable
**Study completion date**: 11-Dec-2012 (last patient completed)
**Study center(s)**: United States (10 centers)

The study was completed as planned.

**Study Objectives**
The primary objective was to evaluate the safety of Xerese topical cream for the treatment of herpes labialis recurrences in immunocompetent children ages 6-11 years of age, following a five-day treatment with five times daily topical administration (i.e. a total of 25 applications).

**Study Events**

- At screening, subjects and their caregivers were trained how to identify the start of a herpes labialis episode, who to contact at the study clinic, and were instructed that treatment should be initiated as early as possible at the first signs or symptoms of a herpes labialis recurrence.
- As soon as possible after experiencing the first signs or symptoms of an episode and treatment start, the subject/caregiver were instructed to contact the study clinic and schedule an in-person visit.
- Phone and/or in-person contacts/visits were to occur every day during the treatment period, with in-person study clinic visits every other day (excluding weekends, if applicable), otherwise by telephone contact.
- Subjects were to have at least one (1) in-person study clinic visit during the treatment period.
- During the treatment period, daily contacts (either phone or in-person) with the clinic were scheduled for assessment of AEs, concomitant medications, and treatment compliance.
- In-person post-treatment (follow-up) visits to the study clinic occurred at:
    - 7 days (± 2 days) after the last dose of treatment
    - 21 days (± 2 days) after the last dose

*Reviewer Comment*

In the original NDA submission, Study 609-07 provided safety data to support approval in adolescents (ages 12-17 years old). Extrapolation of efficacy for Xerese in adolescents was considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and adolescents.

The design of Study MP800 is consistent with the consensus that was reached between FDA and the Applicant prior to the conduct of Study MP800. The schedule of study events for Study MP800 (children ages 6-11 years old) is similar to that for Study 609-07 (adolescents ages 12-17 years old). Study MP800 provides safety data to support approval in children (ages 6-11 years old). Extrapolation of efficacy for Xerese in children ages 6-11 years is considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in children compared to adults.

**7.2 Study Population**

- Key Inclusion Criteria:
  - Male or female, age 6-11 years at time of enrollment
  - General good health, as judged by the Investigator
  - History of recurrent herpes labialis with at least two (2) recurrences during the last twelve (12) months, as based on interview with the subject or subject's caregiver
  - Agreement to refrain from using other topical medical, over-the counter (OTC), or cosmetic products in or around the oral area during the herpes recurrence
  - Agreement to refrain from mechanical disruption of the area affected by herpes labialis during the study recurrence
  - Subjects and their legally acceptable representative(s) must voluntarily sign and date the informed assent (subject) and consent (legally authorized representative)
  - Willingness to comply with all requirements of the study

- Key Exclusion Criteria:
  - Any evidence of an immunosuppressed state of the subject due to underlying disease (e.g. HIV infection) or concomitant treatment (e.g. cancer chemotherapy)
  - Significant skin conditions that occur in the area typically affected by herpes recurrences, and that would interfere with assessment of lesions such as atopic dermatitis, acne, eczema, psoriasis or chronic vesiculobullous disorders
  - Administration of an investigational drug or within 30 days prior to inclusion, or concurrent participation in another research study
  - Administration of an immunomodulatory agent within the past 30 days
  - History of immediate hypersensitivity or serum sickness reaction to any nucleoside analog antiviral agent, or to any topical steroid, or to the vehicle
  - Clinically relevant abnormal physical findings at screening which, in the opinion of the investigator, would interfere with the objectives of the study or that may preclude compliance with the study procedures
  - Nursing or pregnant (Pubescent females require pregnancy testing)

**Baseline Demographics and Baseline Disease Severity**

Baseline demographics and baseline disease severity of the Analysis population (defined as all subjects who applied at least one dose of Xerese, as confirmed by subject diary, or who attended at least one in-person study clinic visit) are summarized in the following table.

**Table 2: Summary of Baseline Patient Demographics and Baseline Disease Severity (Analysis Population[1])**

| Characteristic | Total (N=54) |
|---|---|
| Age at screening (years), n (%) | |
| 6 | 6 (11.1) |
| 7 | 6 (11.1) |
| 8 | 6 (11.1) |
| 9 | 8 (14.8) |
| 10 | 18 (33.3) |
| 11 | 10 (18.5) |
| Mean age (SD) | 9.1 (1.7) |
| | |
| Gender, n (%) | |
| Male | 23 (42.6) |
| Female | 31 (57.4) |
| | |
| Race, n (%) | |
| Caucasian | 49 (90.7) |
| Black or African American | 5 (9.3) |
| | |
| # of Episodes Per Year | |
| Mean | 4 |
| Median (range) | 3 (1, 15) |

[1]Source: Applicant's July 31, 2013 submission.

*Reviewer Comment*
The majority subjects were female (57%) and Caucasian (91%). The mean age was 9 years. Overall, the study population had experienced a clinically significant history of recurrent herpes labialis. Baseline disease severity for recurrent herpes labialis in Study MP-800 was similar to that observed in Study 609-07 (open-label, single-arm, adolescent study; mean – 4 episodes/year, median – 3.5 episodes/year, range 2-15 episodes/year), as well as Study 609-06 (randomized, double-blind, active controlled trial, HIV-1 infected adults; mean – 3.7 episodes/year, median – 3 episodes/year, range 2-10 episodes/year). The baseline disease severity in Study MP800 was less than that observed in Study 609-04 (randomized, double-blind, active-controlled, vehicle-controlled, immunocompetent adults; mean – 5.6 episodes/year, median – 5 episodes/year, range 3-40 episodes/year).

**7.3 Disposition**
Disposition for treated subjects is presented in the following table. A total of 54 subjects developed a recurrence of herpes labialis and received at least one dose of Xerese. Of these 54 treated subjects, 46

(85.2%) completed the study and 8 (14.8%) subjects were discontinued from the study. Three subjects (5.6%) discontinued treatment due to AEs considered related to Xerese by study investigators (see Section 8.4 of this review for additional details).

**Table 3: Subject disposition (analysis population) – Study MP800**

| | Total |
|---|---|
| Subjects treated, n (%) | 54 |
| Completed study, n (%) | 46 (85.2) |
| Discontinued, n (%) | 8 (14.8) |
| Adverse event, n (%) | 3 (5.6) |
| Loss to follow-up, n (%) | 2 (3.7) |
| Consent withdrawn, n (%) | 1 (1.9) |
| Non-compliance with study drug administration, n (%) | 2 (3.7) |

Source: Applicant's July 31, 2013 submission

*Reviewer Comment*
Overall, Xerese is tolerable at the proposed treatment dose and duration (5 times daily for 5 days). Similar to Studies 609-04, 609-06, and 609-07, discontinuations due to AEs were low.

**7.4 Efficacy**
No primary efficacy variables were evaluated in Study MP800 as it was designed to collect safety data. In Study MP800, 49/54 (91%) of children who received Xerese had "normal" skin during the follow-up phase. In Study 609-04, 583/601 (97%) of adults who received Xerese had "normal" skin during the follow-up phase. These descriptive findings suggest the course of disease when treated with Xerese was similar in children and adults.

*Reviewer Comment*
Extrapolation of efficacy for Xerese in children is considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in children compared to adults. This justification had been discussed and agreed with DAVP and PeRC as part of the original NDA submission and this justification had also been discussed and agreed with DAVP and the Applicant during discussions about the study design and prior to the conduct of Study MP-800.

# 8. Safety

This section focuses on the safety data from Study MP800. Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.

**8.1 Exposure**
The exposure data are summarized below:

**Table 4: Exposure to Xerese for study population (n=54)**

| Total number of doses applied, n (%) | |
|---|---|
| Mean (SD) | 22.8 (6.2) |
| Median | 25 |

| | |
|---|---|
| Minimum, Maximum | 2, 30 |

*2 subjects (10/006 and 10/007) did not return the study diary; therefore, no diary data were available for assessment. In both cases, the subject's parent stated that the investigational product had been used once daily on 2 successive days and then discontinued.

*Reviewer Comment*
Similar to Studies 609-04, 609-06, and 609-07, Xerese (five times per day for five days) is associated with high rates of compliance with medication administration.

**8.2 Deaths**
There were no deaths in Study MP800.

**8.3 Nonfatal Serious Adverse Events (SAEs)**
There were no SAEs in Study MP800.

**8.4 Dropouts and/or Discontinuations due to toxicity**
Three subjects (5.6%) discontinued treatment due to AEs considered by study investigators as possibly related to Xerese:

- Subject 03/016 (9 year-old female) reported mild application site pain on Day 2 of treatment and discontinued Xerese on Day 3. The AE resolved following study drug discontinuation; no other interventions were needed.
- Subject 08/014 (11 year-old male) reported moderate rash on Day 3 of treatment and discontinued Xerese on Day 3. Neosporin topical ointment was applied once on Day 3 and parent reported "rash was gone in one hour"; no other interventions were needed.
- Subject 09/003 (11 year-old male) reported mild oral paresthesia on Day 5 of treatment and discontinued Xerese on Day 5. The AE resolved following study drug discontinuation; no other interventions were needed.

*Reviewer Comment*
The case report forms were reviewed. This reviewer agrees with the Applicant's assessment of causality for discontinuations. Overall, no new safety signals were evident from review of discontinuations due to toxicity.

**8.5 Adverse events (AEs)**
Overall, AEs (all grades, all causality) were reported among 8 (14.8%) subjects receiving Xerese. Most AEs were mild and most were considered by study investigators as unrelated to study treatment (Table 5).

**Table 5: AEs (all grades, all causality)[b] reported in ≥1% subjects (n=54)**

| Preferred Term | N (%) |
|---|---|
| Total # of subjects with AE, n (%) | 8 (14.8) |
| Coxsackie viral infection | 1 (1.9) |
| Nasopharyngitis | 1 (1.9) |
| Urinary tract infection | 1 (1.9) |
| | |
| Application site dryness | 1 (1.9) |

| | |
|---|---|
| Application site pain | 1 (1.9) |
| | |
| Lip injury | 1 (1.9) |
| Thermal burn | 1 (1.9) |
| | |
| Oral paresthesias | 1 (1.9) |
| | |
| Pruritus | 1 (1.9) |
| Rash | 1 (1.9) |
| Headache | 1 (1.9) |

[a]Investigator assessment

AEs assessed by investigators to be related to Xerese were reported for 3 subjects (Table 6).

**Table 6: Treatment-Related[b] AEs (all grades) reported in ≥1% subjects (n=54)**

| Preferred Term | N (%) |
|---|---|
| Total # of subjects with AE, n (%) | 3 (5.6) |
| Application site dryness[c] | 1 (1.9) |
| Application site pain[c] | 1 (1.9) |
| Oral paresthesias | 1 (1.9) |
| Pruritus[d] | 1 (1.9) |
| Rash[d,e] | 1 (1.9) |

[b]FDA medical reviewer's assessment of causality
[c]Reported in the same subject (ID# 03/016)
[d]Reported in the same subject (ID# 08/014)
[e]Reported as moderate severity on case report form; all other AEs were mild

*Reviewer Comment*
This reviewer agrees with the investigator assessments of causality. Overall, no new safety signals were evident from review of AEs.

**8.6 Laboratory Findings**
No clinical laboratory evaluations (other than urine pregnancy tests in pubescent females) were performed in Study MP800.

*Reviewer Comment*
No clinical laboratory evaluations were performed in the other phase 3 trials (i.e. Study 609-04, 609-06, and 609-07) for Xerese. The absence of clinical laboratory data is reasonable since Xerese is a topical product with minimal systemic absorption.

**Summary of Safety Findings – Study MP800**
In summary, review of the adverse events and events leading to discontinuation did not definitively reveal any novel adverse events or patterns of events associated with Xerese use in children ages 6-11 years. The overall safety profile of Xerese in children ages 6-11 years appears similar to that previously described for adults and adolescents. Overall, Xerese appears safe for the proposed treatment indication in the proposed patient population.

# 9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

# 10. Pediatrics

As part of the original NDA submission, DAVP and the Pediatric Review Committee (PeRC) agreed to grant a partial pediatric waiver for ages less than 6 years old. Herpes labialis in children under 6 years of age is generally a primary infection, and not a recurrence. Due to the pathophysiology and epidemiology of the disease, Xerese is unlikely to be used in pediatric patients younger than 6 years old.

As part of the original NDA submission, DAVP and PeRC also granted a deferral of the Applicant's pediatric study in children ages 6-11 years old. This supplement does not trigger PREA again since the Applicant already has a waiver. As part of this supplement, DAVP met with PeRC for assessment of this clinical study that was completed as a PREA commitment:

> 1500-1 Deferred pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric patients ages greater than 6 years to less than 12 years.

PeRC concluded that Study MP800 fulfilled the PREA commitment and that no additional studies are needed.

# 11. Other Relevant Regulatory Issues

Post-marketing requirement (PMR) from the Applicant's original NDA submission is fulfilled by the data presented in this sNDA.

Description of required study: Conduct a pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric subjects from 6 to 11 years of age.

| | |
|---|---|
| Protocol Submission Date: | November 2010 |
| Study Initiation Date: | November 2011 |
| Study Completion Date: | November 2012 |
| Final Study Report Submission Date: | May 2013 |

A letter will be sent to the Applicant indicating that this PMR is fulfilled.

# 12. Labeling

The section below includes the major changes to the package insert. Please refer to Sammie Beam's review for all the changes to the package insert. Sponsor's proposed text is in bold font.

**INDICATIONS and USAGE**

Current version: XERESE is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older).

Sponsor's proposal in this supplement: XERESE, a combination of acyclovir and hydrocortisone, is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and **children (6 years of age and older**).

*FDA comment: Sponsor's proposal is acceptable.*

## DOSAGE and ADMINISTRATION

Current version: For each dose, topically apply a quantity of XERESE sufficient to cover the affected area, including the outer margin. Avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection. For adolescents 12 years of age and older, the dosage is the same as in adults.

Sponsor's proposal in this supplement: For each dose, topically apply a quantity of XERESE sufficient to cover the affected area, including the outer margin. Avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection. For **children 6** years of age and older, the dosage is the same as in adults.

*FDA comment: Sponsor's proposal is acceptable.*

## ADVERSE REACTION (Section 6.1)

Current version: The safety data derived from XERESE clinical studies reflect exposure to XERESE in 1002 subjects with recurrent herpes labialis treated 5 times daily for 5 days. The majority of the adverse reactions were local skin reactions and occurred in the area of the application site.

Sponsor's proposal in this supplement: The safety data derived from XERESE clinical studies reflect exposure to XERESE in **1056** subjects with recurrent herpes labialis treated 5 times daily for 5 days. The majority of the adverse reactions were local skin reactions and occurred in the area of the application site.

*FDA comment: Sponsor's proposal is acceptable (Study MP-800 added 54 subjects to the safety database from clinical trials).*

## USE IN SPECIFIC POPULATIONS (Section 8.4 Pediatric Use)

Current version: Safety and effectiveness in pediatric subjects less than 12 years of age have not been established.

Sponsor's proposal in this supplement: Safety and effectiveness in pediatric subjects less than **6** years of age have not been established.

*FDA comment: Sponsor's proposal is acceptable.*

## CLINICAL STUDIES (Section 14.2 Clinical Experience in Pediatric Subjects)

Current version: An open label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4.0 episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50% were female and all were Caucasian. (b) (4) was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety (b) (4) profile appeared similar to that observed in adults.

Sponsor's proposal in this supplement (additional text in bold): **An open label safety study in children with recurrent herpes labialis was conducted in 54 subjects, who averaged an episode of herpes labialis 2 months prior to study entry. The mean age was 9 years (range 6 to 11 years); 57% were female and 90% were Caucasian.** (b) (4) **was applied using the same dosing regimen as in adolescents and adults and subjects were monitored for adverse events and select efficacy parameters. The safety** (b) (4) **profile appeared similar to that observed in adults.**

*FDA Labeling Comments for Sponsor*

Your Study 609-07 (open-label, multi-center, subject initiated safety study) provided safety data to support approval in adolescents (ages 12-17 years). (b) (4)
Extrapolation of efficacy for Xerese in adolescents was considered reasonable based on efficacy data from adults in Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and adolescents.

Your Study MP800 (open-label, multi-center, subject initiated safety study) provided safety data to support approval in children (ages 6-11 years). (b) (4).
Extrapolation of efficacy for Xerese in children was considered reasonable based on efficacy data from adults in

Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in adults and children.

Please revise Section 14 as follows to delete (b) (4) from the following sentences describing Study 609-07 and Study MP800, respectively.

***Sponsor's version:*** *An open label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4.0 episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50% were female and all were Caucasian.* (b) (4) *was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety* (b) (4) *profile appeared similar to that observed in adults.*

***FDA revision (in track changes):*** *An open label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4.0 episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50% were female and all were Caucasian.* (b) (4) *was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety profile appeared similar to that observed in adults.*

***Sponsor's version:*** *An open label safety study in children with recurrent herpes labialis was conducted in 54 subjects, who averaged an episode of herpes labialis 2 months prior to study entry. The mean age was 9 years (range 6 to 11 years); 57% were female and 90% were Caucasian.* (b) (4) *was applied using the same dosing regimen as in adolescents and adults and subjects were monitored for adverse events and select efficacy parameters. The safety* (b) (4) *profile appeared similar to that observed in adults.*

***FDA revision (in track changes):*** *An open label safety study in children with recurrent herpes labialis was conducted in 54 subjects, who averaged an episode of herpes labialis 2 months prior to study entry. The mean age was 9 years (range 6 to 11 years); 57% were female and 90% were Caucasian. Therapy was applied using the same dosing regimen as in adolescents and adults and subjects were monitored for adverse events and select efficacy parameters. The safety profile appeared similar to that observed in adults.*

# 13. Recommendations/Risk Benefit Assessment

From a clinical perspective, the overall safety profile in children ages 6-11 years appears similar to that previously described for adult and adolescent populations. No new safety signals were evident from review of AEs and discontinuations due to toxicity.

From a clinical perspective, extrapolation of efficacy for Xerese in children ages 6-11 years is considered reasonable based on efficacy data from Study 609-04 since the course of recurrent herpes labialis and the effects of Xerese are sufficiently similar in children compared to adults.

Labeling changes were made to the INDICATIONS and USAGE section, DOSAGE and ADMINISTRATION section, ADVERSE REACTION section, USE IN SPECIFIC POPULATIONS section, and CLINICAL STUDIES section.

- **Recommendation for Postmarketing Risk Management Activities**

No postmarketing risk management activities are required for this application.

- **Recommendation for other Postmarketing Study Commitments**

No new postmarketing study commitments are requested for this application.

**APPENDIX**
Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 22-436

Submission Date(s): July 31, 2013

Applicant: Valeant

Product: Xerese (5% acyclovir and 1% hydrocortisone) topical cream

Reviewer: Kirk Chan-Tack, Clinical Reviewer, Division of Antiviral Products (DAVP)

Date of Review: September 18, 2013

Covered Clinical Study (Name and/or Number): MP800

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes √ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 55 (10 priniciple investigators; 45 sub-investigators) | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): None | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A<br>Significant payments of other sorts: N/A<br>Proprietary interest in the product tested held by investigator: N/A<br>Significant equity interest held by investigator in sponsor of covered study: N/A | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes √ | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes √ | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 55 | | |
| Is an attachment provided with the reason: | Yes √ | No ☐ (Request explanation from applicant) |

DAVP Clinical Reviewer Summary: The clinical investigators have no financial interests/arrangements with the Applicant. The Applicant has provided adequate documentation. There are no financial issues

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/s/

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KIRK M CHAN-TACK
12/03/2013

MARY E SINGER
12/03/2013
I concur with Dr. Chan-Tack's recommendations for approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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KIRK M CHAN-TACK
12/16/2013
Sponsor accepted FDA labeling revisions