



Proposal for Reclassification

Application for the reclassification of:

Hydrocortisone 1% w/w when compounded with
aciclovir 5% w/w in primary packs of not more than 2 g
for dermal use

From 'Prescription medicine'

To 'Restricted medicine'

24 July 2017

Submitted by:

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CONFIDENTIALITY

This application contains material supplied in confidence which has been included in the Appendix.

All other confidential material within the application has been identified within square parentheses

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EXECUTIVE SUMMARY

Recurrent herpes labialis is a common skin infection.^{1, 2} Up to 80-90% of adults have serologic evidence of herpes simplex virus (HSV)-1 infection, and recurrent herpes labialis (RHL) occurs in 20-40% of the population.³ Up to 60% of patients experience outbreaks preceded by prodromal symptoms (such as pain, burning, itching, and tingling) at the site where blisters will form.^{4, 5}

The frequency and severity of RHL episodes is variable. Recent data suggest that 35% of patients with RHL experience more than 5 episodes per year; these outbreaks are associated with significant impact on physical, emotional and social well-being.⁶

Episodic antiviral drug therapy has had a modest impact on RHL. An additive effect has been shown when corticosteroids are used in combination with antiviral drugs in herpes zoster, herpes encephalitis and herpes keratitis.⁷

Zovirax Duo represents a new approach to the treatment of RHL. The combination of aciclovir and hydrocortisone curtails viral replication (aciclovir effect) and controls excessive local inflammatory response that occurs during the RHL episode (hydrocortisone effect). Zovirax Duo provides an additional benefit over existing treatments for RHL by being able to prevent recurrences from progressing to ulcerative lesions (defined as the progression into the blister stage of a RHL and beyond) in 42% of subjects (compared with 26% in the vehicle cream control group), without any appreciable increase in risk.^{8, 9} This endpoint has not previously been achieved for any topical RHL treatment. The most desirable outcome for patients with RHL is that a full-blown ulcerative lesion is prevented. Thus the ability of Zovirax Duo to reduce the risk of an episode progressing into an ulcerative lesion meets an important unmet medical need.

Zovirax Duo is indicated for the treatment of recurrent herpes labialis (cold sores), when applied at the first signs or symptoms of a recurrence, to reduce the progression of cold sore episodes to ulcerative lesions and to shorten the healing time of ulcerative lesions, in immunocompetent adults and adolescents (12 years of age and older).

This application seeks an amendment to the current 'Restricted medicine' entry for hydrocortisone in the First Schedule to the Medicines Regulations 1984 and amendments such that the combination product, Zovirax Duo (hydrocortisone 1% w/w compounded with aciclovir 5% w/w) in primary packs of not more than 2 g for dermal use in the treatment of RHL in adults and adolescents (12 years of age and older) will be eligible for supply as a Restricted Medicine.

Non-prescription availability and the associated easier and fast access to Zovirax Duo direct from the pharmacist provides patients the opportunity to initiate early treatment with Zovirax Duo therefore allowing them to optimize treatment outcomes.

The two active ingredients, sold separately, already exist within the confines of the reclassification request and New Zealand consumers have many years' experience with their use:

- Hydrocortisone 1% w/w, either alone or when combined with an antifungal substance, for dermal use has been available as a Restricted Medicine for 27 years.

- Aciclovir 5% w/w or less, as a single active ingredient for dermal use in the treatment of herpes labialis, has been available without prescription for 24 years and in a general sale environment for 15 years.

Each individual active ingredient in Zovirax Duo has a well characterised safety and efficacy profile in their respective indications. The combination product has been available without a prescription in Europe since December 2009 and was registered in Australia as a Schedule 3 Pharmacist Only Medicine in October 2016. Cumulative post-marketing exposure for Zovirax Duo to 31 July 2016 (from prescription and non-prescription sources) was estimated at 3,084,741 patients (assuming one tube per patient) and there were 30 adverse event reports cumulatively to 31 July 2016. To date (21 June 2017) GSK has received 42 reports. The majority of these adverse event reports (39 out of 42) were classed as non-serious. There have been no safety signals identified with non-prescription use of the product to date.

The adverse event profile of Zovirax Duo in clinical trials and available post-marketing experience comprises mainly skin application site reactions. This is consistent with the long established, well characterised safety profiles of the single-active formulations. No significant safety concerns are anticipated based on the current information available.

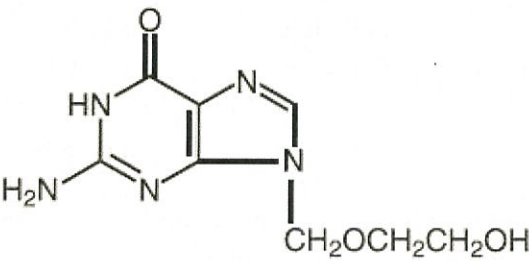
Zovirax Duo has a favourable benefit:risk profile and is suitable for inclusion in the Restricted Medicine classification for hydrocortisone:

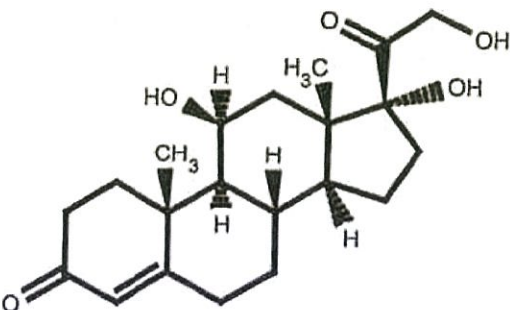
- RHL is very common and there is limited opportunity for mistaken self-diagnosis. The use of Zovirax Duo does not present a risk of masking serious disease if applied in cases of misdiagnosis of the skin lesions.
- Topical application of the whole 2 g tube of Zovirax Duo is unlikely to lead to adverse effects. If the full contents were to be swallowed, the ingested amount of aciclovir (100 mg) is half that contained in a single aciclovir 200 mg tablet (which is prescribed at a dose of 4000 mg per day for herpes zoster). The ingested amount of hydrocortisone (20 mg) would result in plasma levels of hydrocortisone well below endogenous levels.
- An important potential risk for non-prescription Zovirax Duo is off label or inappropriate use. No new information has been received to date of relevance to this potential risk. In the current approved EU Risk Management Plan (RMP), GSK stated that spontaneous adverse event reports associated with off-label use would be evaluated and discussed in the Periodic Benefit Risk Report (PBRER). The adverse events received to date did not reveal any new important safety information regarding off-label/inappropriate use.
- The combination of aciclovir and hydrocortisone provides a unique benefit over existing treatments for RHL by reducing the progression of cold sore episodes to ulcerative lesions, without any appreciable increase in risk.

The data provided within this submission support the favourable benefit-risk profile of Zovirax Duo when used as directed for the treatment of RHL. The most desirable outcome for patients with RHL is that a full-blown ulcerative lesion is prevented. The ability of Zovirax Duo to reduce the risk of an episode progressing into an ulcerative lesion therefore meets an important unmet medical need. The potential risks are low and are no different to those associated with the individual active ingredients which are also in a similar or lower classification to that which is being sought for Zovirax Duo.

PART A

A1. International Non-proprietary Name of the medicine

| | |
|-----------|--|
| Aciclovir |  <p>The chemical structure of Aciclovir is a purine ring system. It features a 2-amino group (H₂N) at position 6, a carbonyl group (C=O) at position 4, and a 2-hydroxyethoxymethyl group (-CH₂OCH₂CH₂OH) attached to the nitrogen at position 9.</p> <ul style="list-style-type: none">• Chemical name: 9-((2-hydroxyethoxy)methyl)-guanine.• Molecular formula: C₈H₁₁N₅O₃.• Molecular weight: 225.• CAS: 59277-89-3. <p>Aciclovir is a white crystalline powder slightly soluble in water and practically insoluble in most organic solvents.</p> |
|-----------|--|

| | |
|----------------|---|
| Hydrocortisone |  <p>The chemical structure of Hydrocortisone is a steroid nucleus with a ketone group at C-3, a double bond between C-4 and C-5, a methyl group at C-10, and a methyl group at C-13. It has hydroxyl groups at C-11, C-17, and C-21, and a 2-hydroxyethyl side chain at C-20.</p> <ul style="list-style-type: none">• Chemical name: 11β, 17α, 21-trihydroxypregn-4-ene-3, 20-dione.• Molecular formula: C₂₁H₃₀O₅.• Molecular weight: 362.5.• CAS: 50-23-7. <p>Hydrocortisone is an odourless, white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in acetone and in alcohol, slightly soluble in methylene chloride, very slightly soluble in ether.</p> |
|----------------|---|

A2. Proprietary name(s)

Zovirax Duo (hydrocortisone 1% w/w compounded with aciclovir 5% w/w)

A3. Name of the company/organisation/individual requesting a reclassification

Applicant's name GlaxoSmithKline Consumer Healthcare
New Zealand Limited

Applicant's Business Address Level 11, Zurich House
21 Queen Street
Auckland 1010
New Zealand

Contact person [REDACTED]
[REDACTED]
[REDACTED]

E-mail Address of contact person [REDACTED]

Postal address of contact person [REDACTED]

Phone Number of contact person [REDACTED]

Fax Number of contact person [REDACTED]

A4. Dose form(s) and strength(s) for which a change is sought

Dose form: cream
Strength: hydrocortisone 1% w/w, aciclovir 5% w/w

A5. Pack size and other qualifications

2 g tube

A6. Indications for which change is sought

Zovirax Duo is indicated for the treatment of recurrent herpes labialis (cold sores), when applied at the first signs or symptoms of a recurrence, to reduce the progression of cold sore episodes to ulcerative lesions and to shorten the healing time of ulcerative lesions, in immunocompetent adults and adolescents (12 years of age and older).

A7. Present classification of the medicine

There are currently 3 classifications for aciclovir in New Zealand:

| Ingredient | Conditions (if any) | Classification |
|------------|--|---------------------|
| Aciclovir | except for external use for the treatment of herpes labialis | Prescription |
| Aciclovir | for external use for the treatment of herpes labialis except in medicines containing 5% or less and in tubes containing 10 grams or less | Pharmacy Only |
| Aciclovir | for external use for the treatment of herpes labialis in medicines containing 5% or less and in tubes containing 10 grams or less | General Sale |

There are currently 3 classifications for hydrocortisone in New Zealand:

| Ingredient | Conditions (if any) | Classification |
|---|---|---------------------|
| Hydrocortisone | except when specified elsewhere in the schedule | Prescription |
| Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone | for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container; in rectal medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or up to 12 suppositories per pack | Restricted |
| Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone | for dermal use in medicines containing 0.5% or less by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container; in rectal medicines containing 0.5% or less by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or 12 suppositories or fewer per pack | Pharmacy Only |

As Zovirax Duo has more than one active ingredient, the active with the most restrictive classification determines the classification of the medicine. Therefore, based on the current classifications for aciclovir and hydrocortisone, Zovirax Duo would be classified as a Prescription Medicine.

A8. Classification sought

GlaxoSmithKline Consumer Healthcare New Zealand Limited requests an amendment to the classification of hydrocortisone 1 per cent (1% w/w) from 'Prescription medicine' to 'Restricted medicine' when compounded with aciclovir 5% w/w in primary packs of not more than 2 g for dermal use in adults and adolescents (12 years of age and older).

The proposal seeks to change only the current 'Restricted medicine' entry for hydrocortisone in the First Schedule to the Medicines Regulations 1984 and amendments.

Current 'Restricted medicine' entry for hydrocortisone:

| Ingredient | Conditions (if any) |
|---|---|
| Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone | for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container; in rectal medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or up to 12 suppositories per pack |

Proposed 'Restricted medicine' entry for hydrocortisone (highlighted in bold red text):

| Ingredient | Conditions (if any) |
|---|---|
| Hydrocortisone and hydrocortisone acetate but no other esters of hydrocortisone | for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient except an antifungal and in a quantity of 30 grams or less or 30 millilitres or less per container; in rectal medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base and in combination with a local anaesthetic and in a quantity of 35 grams or less per container or up to 12 suppositories per pack; for dermal use in medicines containing 1% or less but more than 0.5% by weight of hydrocortisone base with no other active ingredient except aciclovir (5% w/w or less) in adults and adolescents (12 years of age and older) and in a quantity of 2 grams or less per container |

A9. Classification status in other countries (especially Australia, UK, USA, Canada)

Medivir first obtained approval for Aciclovir-hydrocortisone Cream in July 2009 in the USA. The first EU non-prescription approval for Zovirax Duo via the Decentralised Procedure (DCP) with Sweden as the Reference Member State (Ref: SE/H/882/01/DC) was approved in December 2009. A Repeat Use Procedure including additional 17 European countries has been approved the 1st of March 2017 and the National Phase of the procedure has been concluded in the majority of the Concerned Member States. In Australia, Zovirax Duo was approved by the TGA in October 2016 as a Schedule 3 (Pharmacist Only) medicine.

To date, the Zovirax Duo combination product has been approved for non-prescription use in twenty-two markets (Table 1). In addition, the product has also been approved in six markets as a prescription only medicine and in three of them a switch application from prescription to non-prescription is under Health Authorities evaluation.

Table 1. Classification status of Zovirax Duo in other countries

| Country | Classification Status |
|----------------|--|
| Australia | OTC via pharmacist |
| Austria | Rx |
| Belarus | Rx |
| Belgium | Rx* |
| Bulgaria | OTC |
| Croatia | OTC |
| Cyprus | Repeat Use European Procedure - National phase pending |
| Czech Republic | OTC |
| Denmark | OTC |
| Estonia | OTC |
| Finland | OTC |
| France | Rx* |
| Germany | OTC** |
| Greece | Repeat Use European Procedure - National phase pending |
| Hungary | OTC |
| Iceland | OTC |
| Ireland | Rx |
| Kazakhstan | OTC |
| Latvia | OTC |
| Lithuania | OTC |
| Luxembourg | Repeat Use European Procedure - National phase pending |
| Malta | Repeat Use European Procedure - National phase pending |
| Netherlands | OTC |
| Norway | OTC |
| Poland | OTC |
| Portugal | OTC |
| Romania | Repeat Use European Procedure – National Phase Pending |

| | |
|--------------------|--|
| Russian Federation | OTC |
| Slovakia | OTC |
| Slovenia | Repeat Use European Procedure – National Phase Pending |
| Spain | OTC |
| Sweden | OTC |
| Ukraine | OTC |
| United Kingdom | Rx* |

* Switch application from Rx to OTC is pending in this country

**German Ministry of Health Switch Committee approved the OTC status for the combination of active. Publication on the public gazette pending.

A10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute

There is currently no information on the extent of usage in New Zealand as Zovirax Duo does not currently have consent to distribute in New Zealand.

Estimating patient exposure for OTC products is inherently difficult. Based on internal GSK sales volume data, approximate global sales of Zovirax Duo assuming that a single 2 gram tube of cream is used to treat one cold sore episode by a single patient, equates to an estimated cumulative patient exposure to Zovirax Duo to 3,084,741 episodes treated.

A11. Labelling or draft labelling for the proposed new presentation(s)

Summary of product details

| | |
|---------------------|--|
| Active ingredients | <ul style="list-style-type: none"> ▪ Aciclovir 5% w/w ▪ Hydrocortisone 1% w/w |
| Formulation | <ul style="list-style-type: none"> ▪ Topical cream |
| Indication | <ul style="list-style-type: none"> ▪ Treatment of recurrent herpes labialis (cold sores), when applied at the first signs or symptoms of a recurrence, to reduce the progression of cold sore episodes to ulcerative lesions and to shorten the healing time of ulcerative lesions, in immunocompetent adults and adolescents (12 years of age and older) |
| Dosage | <ul style="list-style-type: none"> ▪ Topical administration only. ▪ Adults and adolescents over 12 years of age. ▪ To be applied five times a day, approximately four hourly omitting the night time application. ▪ Not recommended for use in children under 12 years of age. |
| Length of treatment | <ul style="list-style-type: none"> ▪ 5 days |
| Pack size | <ul style="list-style-type: none"> ▪ 2 g |

The Zovirax Duo product will be presented in a sealed tube which will be housed in an outer cardboard carton. A copy of the proposed tube and carton artwork is provided in Appendix 1 of this application.

The carton and Consumer Medicine Information (CMI) will clearly specify the indication/site of application (cold sores) and that the product should not be used in the eyes, and inside the mouth or nose.

Clear dosing instructions are proposed for the carton and CMI, regarding frequency (5 times a day) and duration of use (for up to 5 days).

A12. Proposed warning statements

A proposed Data Sheet (DS) and CMI have been developed for specific use with the Zovirax Duo product. Draft copies of these documents are provided in Appendix 1 of this application.

The proposed CMI will include:

- warnings which clearly specify that the product is to be applied to cold sores on lips and face, and that the product should not be used in the eyes, inside the mouth or nose, and also that the product is not for use on the genitals
- wording to advise patients to seek medical advice if lesions are still present after 10 days, while still reinforcing the message that the duration of treatment is limited to 5 days.

The sponsor considers that seeking advice after 10 days rather than 5 days is more appropriate for a patient with cold sores given that the mean episode duration (time to loss of crust) for subjects with ulcerative episodes treated with the product was 5.7 days in the pivotal clinical study. (The 3rd quartile was 7.5 days and the maximum episode duration was 20.5 days.)

The proposed DS includes adverse reactions that have been reported for aciclovir cream:

- Angioedema: The Global Datasheet for aciclovir cream includes “immediate hypersensitivity reactions including angioedema” as a very rare adverse reaction.
- Itching and stinging have been added to the list for Zovirax Duo, both of which have been reported for aciclovir cream as uncommon reactions.

A13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

There are no products available in New Zealand containing the same combination of active ingredients (aciclovir and hydrocortisone).

Single active cream products containing aciclovir and hydrocortisone that are available in New Zealand will not be affected by the proposed reclassification of the combination product.

PART B: Reasons for requesting classification change including benefit-risk analysis

B1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Benefits summary

RHL is a recurrent episodic disease which causes physical pain, considerable physiological discomfort, and social distancing. Zovirax Duo provides a unique benefit over existing treatments for RHL by reducing the progression of cold sore episodes to ulcerative lesions when applied at the early signs and symptoms of cold sore recurrence. In those who develop ulcerative lesions, Zovirax Duo still results in an improvement in healing time, similar as with single active antiviral topical treatments. Reclassification of Zovirax Duo and the associated easier access to Zovirax Duo direct from the pharmacist will provide patients with the opportunity to treat a RHL episode before an ulcerative lesion develops, and thus to benefit from the treatment outcomes reducing the burden of distress. Reclassification will also save consumers time by avoiding the need to consult a physician and obtain a prescription and also save healthcare system costs.

Background: Natural history and pathology of recurrent herpes labialis

RHL is a common skin infection that is almost always associated with HSV-1 infection.^{1,2} Primary HSV-1 infection usually occurs in the oral cavity and may be asymptomatic or result in herpetic gingivostomatitis. Compared with symptomatic primary infection, recurrent episodes are milder and shorter in duration with minimal systemic involvement.

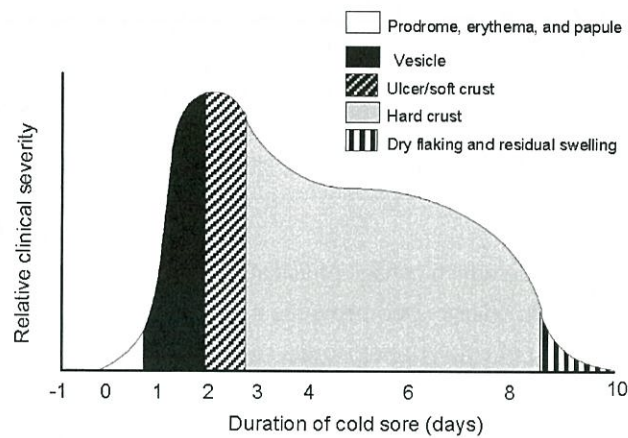
Most subjects are infected with HSV-1 between 6 months and 14 years of age, and typically before the age of 5 years.¹⁰ Infection with HSV-1 is common throughout the world and prevalence steadily increases with age. Up to 80-90% of adults have serologic evidence of HSV-1 infection, and RHL occurs in 20-40% of the population.³ The point prevalence (at any given time point) has been estimated to be approximately 1.6-3.0%.^{11,12}

Up to 60% of patients experience outbreaks preceded by prodromal symptoms (such as pain, burning, itching, and tingling) at the site where blisters will form.^{4,5} This immediately identifies them as associated with RHL, which is confirmed if an ulcerative lesion subsequently develops. An ulcerative recurrence in untreated subjects develops through eight stages over a period of approximately 10 days.¹⁰

The frequency of RHL outbreaks varies in affected individuals from rare episodes every 5-10 years in some individuals to monthly or more frequent episodes among a small proportion of individuals.¹⁰ Cold sores manifest as mucocutaneous lesions on the lip, nose or face. The severity is extremely variable, ranging from minimal discomfort to extensive lesions on the lips, nose and cheeks. Recent data suggest that 35% of patients with RHL experience more than 5 episodes per year; these outbreaks are associated with significant impact on physical, emotional and social well-being.⁶

Recurrent episodes that progress to vesicles that rupture to form painful ulcers (ulcerative recurrence, also called classical cold sores) cause considerable discomfort and psychosocial distress. Disease progression is rapid, with episodes achieving maximum clinical severity within about 2 days (Figure 1).

Figure 1. Duration and severity of different stages of a RHL episode.



Data are those of placebo-treated patients in a clinical trial.
 Reprinted from Spruance *et al. Semin Dermatol.* 1992;11:200.

Following primary infection of the oral mucosa, HSV-1 ascends through sensory nerve axons and establishes a chronic, latent infection in sensory ganglia.¹³ Unlike many other common viral infections, herpes viruses persist for the lifetime of the host they infect.

The virus reactivates periodically and returns to the periphery through the axons of sensory neurons to replicate in mucocutaneous tissues. Reactivation of HSV-1 can occur as asymptomatic shedding in secretions such as saliva, and/or as the development of clinical lesions. Recurrent lesions most frequently develop on the lower lip, but can also be found on the upper lip, nose, cheek, chin, within the oral cavity (gingiva and hard palate), and eyelid. The frequency of recurrences ranges from regular monthly outbreaks in some to rare episodes every few years in others. About 30% of the population experience more than one episode every other year and 7% experience three or more episodes annually. Genetic susceptibility, immune status, age, anatomic site of infection, initial dose of inoculums, and viral subtype may influence the frequency of recurrences.^{14,15}

Compared with the primary infection, RHL is milder and shorter in duration, with minimal systemic involvement. The severity of RHL is extremely variable, ranging from minimal symptomatic discomfort to extensive lesions on the lips, nose, and cheeks. Frequent outbreaks are associated with significant inconvenience, pain, cosmetic disfigurement, and psychological distress.

Up to 60% of patients experience RHL preceded by prodromal symptoms (e.g. such as pain, burning, itching, and tingling) at the site where blisters will form.^{4,5} These symptoms last nearly 6 hours and are triggered by early viral replication near the sensory nerve endings in the basal cell layer of the epidermis.

In RHL, viral replication is most active in the 8 hours after the onset of an episode.¹⁶ This is followed by an immune response that curtails the infection and is believed to contribute to the clinical features of the disease: erythema, swelling, and ulceration.¹⁷ The immune response, triggered by HSV replication, contributes to herpes lesion pathology by local infiltration of NK cells and CD4 and CD8 positive T-cells.^{18,19}

An ulcerative RHL episode develops through eight stages over a period of approximately 10 days:¹⁵

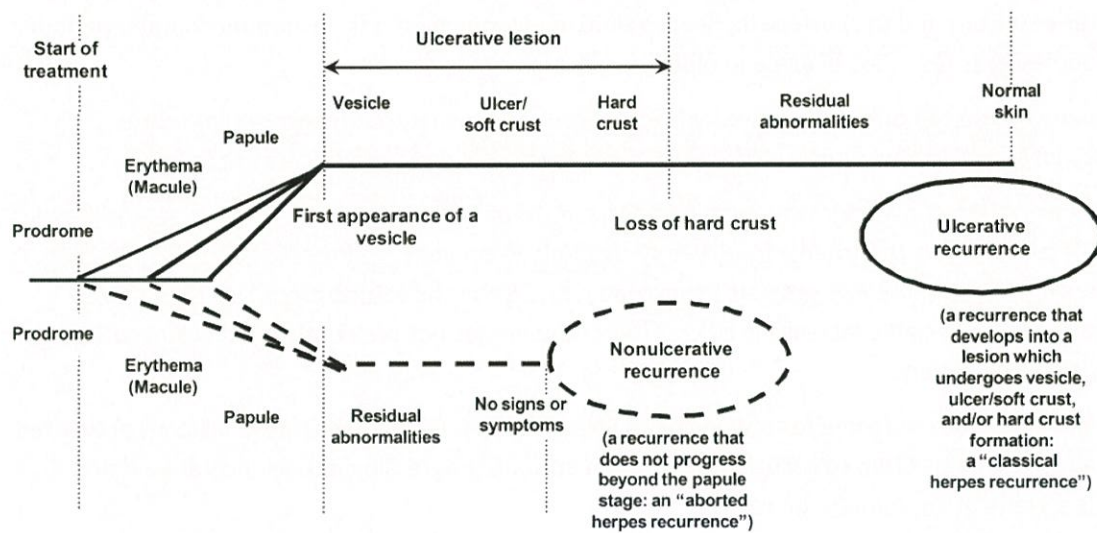
Prodrome → erythema → papule → vesicle → ulcer/soft crust → hard crust → residual abnormalities → normal skin

The prodromal symptoms of RHL typically develop on the lips or surrounding areas. This immediately identifies them as associated with RHL, which is confirmed if an ulcerative lesion subsequently develops.

The most notable stages for the patient are painful, visible vesicles with subsequent ulcers and crusting. Pain and discomfort are most pronounced at the vesicle and ulcer stages, and resolve over 4 to 5 days.

Some maculo-papular lesions never progress beyond the papule stage (non-ulcerative recurrences) and thus never become ulcerative lesions (Figure 2)²⁰. In clinical practice, these may account for as many as 25% of all recurrences.^{1, 21}

Figure 2. Stages of a RHL.



Rationale for combining a topical antiviral with a low potency corticosteroid

Virus replication occurs early after the onset of an episode and is followed by an immune response that is thought not only to curtail the infection but also to contribute to the clinical features of the disease: erythema, swelling and ulceration.

Topical aciclovir is well proven to accelerate healing and reduce the duration of pain in patients with RHL. Although hydrocortisone alone is not indicated for the treatment of RHL, its use in the management of a variety of inflammatory skin conditions is very well established.

Episodic antiviral drug therapy has had a modest impact on RHL. Currently available episodic therapies, such as 5% aciclovir cream, provide a reduction in the healing time of RHL of between 0.5 to 1 day and an improvement in symptoms. However, despite several large studies with aciclovir 5% cream monotherapy using prevention of ulcerative lesions as either a primary or secondary endpoint, a statistically significant difference from the vehicle control has not been established.

Corticosteroids have anti-inflammatory and immunosuppressive effects²²⁻²⁴ and have often been used as an adjunct to anti-infective agents. An additive effect has been shown when used in combination with antiviral drugs in herpes zoster, herpes encephalitis and herpes keratitis.⁷ In

further support of this, anti-inflammatory drugs in combination with antivirals have been shown to be beneficial in a murine model of recurrent HSV disease.^{25,26}

Zovirax Duo represents a new approach to the treatment of RHL: The combination of aciclovir and hydrocortisone targets both of the pathogenic mechanisms involved in RHL; aciclovir curtails viral replication and hydrocortisone controls excessive local inflammatory response that occurs during a recurrent episode of HSV infection. Non-prescription availability of Zovirax Duo will provide patients with the potential to begin treatment when symptoms arise and before blisters have developed, with the added benefit of reducing the likelihood of the initial symptoms developing into ulcerative lesions.

Zovirax Duo fulfils an unmet medical need

Zovirax Duo is indicated for the treatment of recurrent herpes labialis (cold sores), when applied at the first signs or symptoms of a recurrence, to reduce the progression of cold sore episodes to ulcerative lesions and to shorten the healing time of ulcerative lesions, in immunocompetent adults and adolescents (12 years of age and older).

In common with the other available single active topical antiviral treatments for cold sores (penciclovir and aciclovir cream), Zovirax Duo improves healing time of ulcerative lesions.

The combination of aciclovir with hydrocortisone in Zovirax Duo provides an additional/new/unique benefit over existing treatments for RHL by being able to prevent recurrences from progressing to blisters and ulcers in 42% of subjects (compared with 26% in the vehicle cream control group), without any appreciable increase in risk.^{8,9} This endpoint has not previously been achieved for any topical RHL treatment.

The most desirable outcome for patients with RHL is that a full-blown ulcerative lesion is prevented. The ability of Zovirax Duo to reduce the risk of an episode progressing into an ulcerative lesion meets an important unmet medical need.

Benefit of improved access

Data from the pivotal study highlight the importance of early intervention with Zovirax Duo.^{8,9} Ulcerative lesions did not develop in 46% of subjects who started to treat at the prodrome stage compared with 37% and 33% at the erythema and papule stages, respectively. This trend was statistically significant (Cochrane-Armitage trend test; $p=0.023$). Reduced risk of lesion development has not been demonstrated with existing single active antiviral treatments. Therefore, the non-prescription availability of Zovirax Duo provides an additional benefit over existing products.

Minimising barriers to access is particularly relevant for cold sore sufferers because of the need for initiating early treatment with Zovirax Duo for optimal results. Episodes that progress to unsightly blisters, ulcer and scabs are a source of embarrassment and physical and emotional discomfort in many sufferers from RHL. Non-prescription availability and the associated easier and quicker access to Zovirax Duo direct from the pharmacist is likely to give patients greater opportunity to initiate early treatment, and thus to optimise the treatment outcomes.

B2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk

The sponsor's Zovirax Duo has been available as a non-prescription product in Europe since January 2010. Both of the active ingredients (aciclovir 5% w/w and hydrocortisone 1% w/w) and all

excipients of the combination formulation are widely used and the safety of these individual ingredients is well-characterised.

The strength, dose and route of administration of aciclovir in the combination product, Zovirax Duo, are the same as for existing aciclovir 5% cream. Both products are indicated for the treatment of cold sores and the target patient group for Zovirax Duo is included within the target patient group for aciclovir 5% cream. Products for dermal use which combine hydrocortisone 1% with miconazole (e.g. Resolve Plus) or clotrimazole (e.g. Canesten Extra) are available and well-established in New Zealand as Restricted Medicines. To date there have been no identified safety issues with non-prescription use of Zovirax Duo, and it continues to have a favourable benefit-risk profile.

Potential for medication errors

No significant safety information on patterns of medication errors or potential medication errors was identified from clinical and/or post-marketing sources for Zovirax Duo.

Characterisation of potential risks

The important potential risk for Zovirax Duo is inappropriate usage outside the indicated population:

- Children under 12 years of age
- Use in immunocompromised patients
- Use on an inappropriate application site (e.g. mucous membranes, including inside the mouth, nose, eyes or genitals)
- Treatment of non-HSV disease (e.g. acne)
- Chronic use (more than 5 days).

Based on the limited systemic exposure (see section B6) and nature of the product (e.g. small pack size), there are unlikely to be any safety issues associated with these potential risks.

Masking symptoms or delaying diagnosis of a more serious condition has not been an issue for aciclovir 5% cream, which has been available general sale in New Zealand for 15 years. Zovirax Duo will be used for the same indications and thus it is unlikely to present a problem, particularly given supply under the supervision of a Pharmacist.

Risk minimisation strategies

There is a very low potential for harm from misuse with the Zovirax Duo. The strength, dose, and route of administration of aciclovir in Zovirax Duo is the same as in aciclovir 5% cream; the strength and route of administration of hydrocortisone in the combination is the same as in hydrocortisone 1% cream. The limited need for risk mitigation will be achieved through the safety messages in the packaging and CMI and the involvement of the Pharmacist at the point of purchase.

The packaging and leaflet are designated as the main risk minimisation tools, the safety messages from therein will be reflected in any associated communication and education materials:

- Zovirax Duo is indicated for use on cold sores, and the product is applied to cold sores on the lips and face.
- It is not recommended for application to the mucous membranes such as eyes, inside the mouth or nose. It is not to be used to treat genital herpes.

- Zovirax Duo is to be used on the affected area 5 times a day, for five days; if symptoms worsen or do not improve after 10 days, patients should discontinue treatment and seek medical advice.
- It is not recommended for use in patients who know that they are immunocompromised. Even though the safety of Zovirax Duo has been established in mild to moderately immunocompromised subjects,²⁷ the product is not intended for use in this group. The scope of the Warnings statement in the proposed Data Sheet for individuals who know that they are immunocompromised has been expanded to include all such individuals (and not limited to severely immunocompromised). Individuals who know that they are immunocompromised are encouraged to consult a doctor concerning the treatment of any infection.
- It is not to be used in children under 12 years of age.
- Sales will be restricted to pharmacies and only after discussion with a Pharmacist.
- Routine risk minimisation measures are considered sufficient as per EU Risk Management Plan (RMP). No additional risk minimisation measures are considered necessary.

B3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

RHL is very common, and this fact alone makes it a readily recognisable condition.

RHL is an established and easily identified indication for self-assessment. The prodromal symptoms that often herald an episode of RHL and the distinct appearance and typical location of recurrences on the lips or around the lip margins, reduce the risk that the condition would be mistaken for other dermatological conditions on the face.

Self-treatment of RHL with general sale aciclovir 5% w/w has been possible in New Zealand for 15 years. Importantly, the characteristic signs and symptoms associated with the early stages of a cold sore are recognised by many sufferers, and so can prompt early intervention with Zovirax Duo, which is critical to maximise the likelihood of preventing the development of ulcerative lesions.

B4. Relevant comparative data for like compounds

Episodic antiviral drug therapy has had a modest impact on RHL. Currently available episodic therapies, such as 5% aciclovir cream, provide a reduction in the healing time of RHL of between 0.5 to 1 day and an improvement in symptoms. However, despite several large studies with aciclovir 5% cream monotherapy using prevention of ulcerative lesions as either a primary or secondary endpoint, a statistically significant difference from the vehicle control has not been established.

Corticosteroids have anti-inflammatory and immunosuppressive effects²²⁻²⁴ and have often been used as an adjunct to anti-infective agents. Although hydrocortisone alone is not indicated for the treatment of RHL, its use in the management of a variety of inflammatory skin conditions is very well established. An additive effect has been shown when used in combination with antiviral drugs in herpes zoster, herpes encephalitis and herpes keratitis.⁷ In further support of this, anti-inflammatory drugs in combination with antivirals have been shown to be beneficial in a murine model of recurrent HSV disease.^{25,26}

Zovirax Duo combines aciclovir with hydrocortisone; thus it targets both of the pathogenic mechanisms involved in RHL. Non-prescription availability of Zovirax Duo will provide patients with

the potential to begin treatment when symptoms arise and before blisters have developed, with the added benefit of reducing the likelihood of the initial symptoms developing into ulcerative lesions.

Aciclovir and hydrocortisone: clinical data

The results from the pivotal Phase III study showed that application of Zovirax Duo initiated at an early (prodrome, erythema, papule) phase:^{6,8,9}

- Prevented the progression of cold sore episodes to ulcerative lesions in 42% of subjects. This was statistically significantly higher than the proportion of subjects in the aciclovir 5% w/w in vehicle cream (35%, $p = 0.014$) and vehicle cream alone (26%, $p < 0.0001$) groups.
- In those subjects that developed ulcerative lesions, the mean episode duration was 5.7, 5.9, and 6.5 days, for Zovirax Duo Cream, aciclovir in vehicle cream, or vehicle cream alone, respectively ($p=0.008$ for the comparison between Zovirax Duo Cream with vehicle cream alone).

Conversely, the potential disadvantages of a fixed-dose combination (that it may meet the needs of the average patient, but is unlikely to be ideally adjusted for the needs of each individual, and that there is the potential for additive adverse reactions specific to each substance) have not been borne out in clinical trials:

- No increase in the already low rate of resistance to aciclovir has been observed (see Section B8 for details)
- Similar adverse event profiles for the combination and aciclovir 5% cream (see Section B9 for details).
- Overall, the nature and frequency of adverse events did not differ significantly between Zovirax Duo, aciclovir in the vehicle cream, and vehicle cream alone (see Section B9 for details).

B5. Local data or special considerations relating to New Zealand

Whilst the combination of aciclovir and hydrocortisone is not currently available in New Zealand, there is extensive post-marketing experience with aciclovir and hydrocortisone as individual active ingredients. Results from the SMARS (Suspected Medicine Adverse Reaction Search) database show that there were 51 adverse events reported (from 30 reports) and 137 adverse events reported (from 68 reports) for hydrocortisone and aciclovir respectively during the period between 1 January 2000 and 30 April 2017. There were no deaths reported. Whilst the information from SMARS is limited (please refer to <http://medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp> for further information), it does provide an indication that the incidence of adverse events for the individual active ingredients is low which is consistent with the favourable safety profiles of the ingredients globally.

B6. Interactions with other medicines

No interaction studies have been conducted with Zovirax Duo because it is administered topically and systemic absorption is minimal. The potential for clinically relevant drug-drug interactions is therefore remote.

In assessing the potential for systemic absorption of aciclovir and hydrocortisone from Zovirax Duo, there are two critical considerations:

- A very small part of the human body, around 1 cm², is exposed to Zovirax Duo during treatment.
- Each 2 g tube of Zovirax Duo contains 100 mg aciclovir and 20 mg hydrocortisone.

Topical application of aciclovir results in undetectable to minimal systemic absorption. Systemic exposure to aciclovir has been studied after application of aciclovir 5% cream five times daily for 4 days in six subjects.²⁸ Aciclovir plasma concentrations 1 hour after the last application were below the detection limit in five subjects and barely detectable in one subject; mean urinary excretion was 0.06% of the applied dose. Therefore, systemic exposure of aciclovir during Zovirax Duo treatment will be minimal.

Like aciclovir, hydrocortisone is poorly absorbed following topical application. In common with many other topically applied substances, the stratum corneum is the major barrier to the penetration of hydrocortisone into the skin, and often only around 1% of the applied dose penetrates.^{29,30} The degree of skin penetration may vary according to the vehicle used,^{31,32} the thickness and structure of the skin at the site of application,³³ and whether the site is occluded.³⁴ However, the penetration and efficacy of hydrocortisone in topical formulations were not significantly affected when combined with different antibiotics.^{35,36}

There is an increased risk of systemic absorption when an occlusive dressing is used, and this is recognised as an issue for hydrocortisone. The likelihood of someone using Zovirax Duo in conjunction with a cold sore patch product is considered to be low and the potential risks, should this happen, are also considered to be low given the low potency of hydrocortisone, limited application area and limited duration of treatment. Nonetheless, an appropriate warning to advise patients not to cover the cold sore area is provided in the proposed product labelling.

The two active ingredients, aciclovir and hydrocortisone, have totally different modes of action, and dose adjustments based on combined efficacy or safety were therefore not deemed necessary. The individually established efficacious concentrations were used in the combination product. Food-drug interactions are not relevant due to the topical application of the combination product.

B7. Contraindications and precautions

Contraindications

Zovirax Duo is contraindicated for use:

- in patients with known history of hypersensitivity to aciclovir, valaciclovir, hydrocortisone, or any of the excipients
- in skin lesions caused by any viruses other than HSV, or for fungal, bacterial or parasitic skin infections.

During the clinical development of Zovirax Duo, hypersensitivity reactions due to the active ingredients or excipients in the Zovirax Duo formulation were rare.

Although considered unlikely, certain orofacial lesions (e.g. acne, boils, warts, insect bites, shingles, or impetigo) might be confused with RHL. Such use is unlikely to be associated with safety issues given limited systemic absorption and the small pack size (2 g).

Precautions:

- Zovirax Duo is to be applied to cold sores on the lips and face. It is not recommended for application to mucous membranes (e.g. in the eye, or inside the mouth or nose). Not to be used for genital herpes. Particular care should be taken to avoid contact with the eye.
- Patients with particularly severe recurrent herpes labialis should be encouraged to seek medical advice.
- Not to be used with occlusive dressings, such as plasters or specialised cold sore patches/plasters. The use of occlusive dressings has the potential to increase the absorption of hydrocortisone and therefore increase the risk of skin irritation and systemic effects. Patch products are available that are specifically designed to be placed over a cold sore to promote healing. A warning is included in the proposed PI, a copy of which is included in Appendix 1 of this application, to help ensure that patients do not use these types of products or other occlusive dressings with Zovirax Duo. The current package leaflet already includes this warning.
- Zovirax Duo is not intended for use in patients who are immunocompromised. Infections in immunocompromised patients, including episodes of recurrent herpes labialis, may be more severe than in immunocompetent patients and it is therefore advisable that a physician manages the treatment of any infection.
- Long-term continuous use should be avoided; Zovirax Duo should not be used for longer than 5 days.
- Zovirax Duo contains cetostearyl alcohol, which may cause local skin irritations (e.g. contact dermatitis), and propylene glycol, which may cause skin irritation.
- The use of Zovirax Duo in pregnancy should be considered only when the potential benefits outweigh the possibility of unknown risks. However, the systemic exposure to aciclovir and hydrocortisone from topical application of the cream is very low. A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst subjects exposed to aciclovir compared with the general population and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Systemic exposure to aciclovir from topical application of aciclovir cream is very low.

Use of hydrocortisone on the face

Prolonged application of corticosteroids to the face is undesirable. Corticosteroids can cause skin damage, although this problem is not known to occur commonly with hydrocortisone, a low potency corticosteroid.³⁷

An American Academy of Dermatology (AAD) guideline for the use of topical corticosteroids has also addressed the issue of application to the face.³⁸ Whilst the face is particularly susceptible to local side effects of corticosteroids because of the thin stratum corneum, side effects are rare with the use of low potency topical corticosteroids.³⁸ The AAD guideline confirms that prolonged use should be avoided, but it does not prohibit use on the face.

Although the risks are considered to be low, it is anticipated that a range of educational materials will be available to pharmacists at the time of the launch to help guide appropriate recommendation. These materials will reinforce the safety messages provided in the proposed Data Sheet and CMI. The training materials will also explain to pharmacists why it is acceptable to use

topical hydrocortisone in combination with aciclovir to treat a viral infection on the face as this may conflict with previous information on the use of topical corticosteroids. An example of professional education materials prepared for use in European markets is provided in Appendix 1 of this application.

With the use of Zovirax Duo for only 5 days, there are no issues with the very low dose (20 mg per tube) of hydrocortisone on the lips and area immediately around them on the face. The small pack size will limit the opportunity for chronic use. As noted previously, chronic use is considered unlikely based on pack presentation, and associated effects are considered unlikely based on limited systemic absorption.

B8. Possible resistance

Zovirax Duo under the proposed conditions for use is unlikely to pose a risk to the individual or to the community due to development of aciclovir-resistant HSV. The risk of an increased incidence of HSV resistance to aciclovir among subjects treated with Zovirax Duo is low. The potential for development of aciclovir-resistant HSV is described below.

Experience with aciclovir

The experience from decades of aciclovir use in millions of patients, with prescription-only and non-prescription topical and oral treatments, clearly shows that rates of aciclovir resistance are low in immunocompetent patients and have not increased over the years.^{39,40} This situation is very different to the experience with antibiotics, antifungals, and other antivirals (e.g. those used to treat human immunodeficiency virus or influenza). In these cases, the prevalence of resistance generally increases over time, is frequently associated with clinical disease or treatment failure, and person-to-person transmission of resistant organisms may occur.

There are only isolated reports of aciclovir resistance in patients receiving systemic corticosteroids prior to commencement of aciclovir treatment.^{41,42} However, based on data from the clinical development programme for Zovirax Duo or from clinical experience in patients with herpes keratitis, there is no evidence to suggest that the risk of resistance increases among patients in whom steroids are commenced concurrently with aciclovir. Topical steroids have been used to mitigate pathogen-induced inflammation under antiviral cover in patients with herpes keratitis for many years and this combination is the current mainstay of therapy for HSV stromal keratitis.⁴³ However, there has been no increase in the prevalence of antiviral-resistant HSV in this group of patients.

Antiviral resistance and Zovirax Duo

There is a theoretical risk that suppression of the immune system with a glucocorticoid might increase HSV replication through promotion of viral replication or reduced immune clearance of virus and lead to a more severe infection, and thereby promote the development of resistance. This view, however, is not supported by results from cell culture systems, animal experiments, clinical experience,⁴² and observations on viral yield and aciclovir resistance in the clinical development programme of Zovirax Duo (Study No. 609-04,⁸ Study No. 609-06,²⁷ and Study No. 98-609-013⁴⁴).

In the treatment of RHL, Zovirax Duo is applied five times daily for 5 days only. The plasma levels of hydrocortisone generated by these applications will be lower than normally circulating levels of the endogenous hormone. Thus the plasma levels of hydrocortisone which are achieved during normal

use of Zovirax Duo should not cause any degree of systemic immunosuppression, and therefore not increase the risk of the emergence of antiviral resistance. Moreover, the fixed-dose combination ensures that there is aciclovir cover on any areas of skin where hydrocortisone could theoretically limit the local immune response.

No aciclovir-resistant virus was identified in immunocompetent or immunocompromised subjects during the clinical development programme for Zovirax Duo. There was no evidence of enhanced virus replication in immunocompromised subjects with ulcerative recurrences who were treated with Zovirax Duo in Study No. 609-06.²⁷ The frequency of HSV-positive lesions was comparable between the two treatment groups (29% in the Zovirax Duo group and 27% in the aciclovir in vehicle group). Importantly, no aciclovir-resistant virus was identified in this study population. The safety profiles for the two treatments were also similar.

There was no evidence of enhanced virus replication in immunocompetent subjects with ulcerative recurrences who were treated with Zovirax Duo in Study 609-04: the frequency of HSV-positive lesions was comparable between the two treatment groups (22% in the Zovirax Duo group and 24% in the aciclovir in vehicle cream group).⁸ Moreover, the proportion of virus-positive subjects among those with a lesion duration >5.5 days was also very similar for these two treatment groups being 19/78 subjects (24.4%; Zovirax Duo) and 29/107 (27.1%; aciclovir in vehicle cream), respectively (see Table 14.3.4.4 in the study report for ME609-04). These results show very clearly that the inclusion of hydrocortisone did not increase HSV replication.

B9. Adverse events - nature, frequency, etc

Although the combination of aciclovir and hydrocortisone is new, the individual components are well-established. Each individual active ingredient in Zovirax Duo has a well characterised safety and efficacy profile in their respective indications, as well as a combination product.

Both topical 5% aciclovir cream and topical 1% hydrocortisone cream and ointment have been available for many years (approximately 30 years on the market for aciclovir 5% cream, and over 50 years on the market for 1% hydrocortisone cream) and have large cumulative post-marketing exposures. No significant safety concerns are anticipated based on the current information available on the individual active ingredients.

Routine pharmacovigilance is considered adequate to monitor the adverse event profile of Zovirax Duo and to identify any new safety concern in the non-prescription environment, including the possible risk of off-label use. For details refer to the EU Risk Management Plan in Appendix 1 of this application.

The adverse reaction profile in clinical trials and post marketing data comprises mainly of application site reactions such as skin drying or flaking, and more uncommonly transient burning, tingling or itching. This is consistent with the long, well established safety profiles of both individual-actives.

Data from safety studies

The safety of Zovirax Duo has been assessed in ten studies: five skin blanching/dermal/photosafety studies (Phase I); one Phase II study; and four Phase III studies (Table 2, next page).

Adverse events were reported more commonly in the Phase II study in which HSV recurrences were induced using ultraviolet radiation than in the Phase III studies where “natural” recurrences were studied (Table 3, next page). In the Phase III studies, no adverse events were reported in the

majority (> 80%) of subjects. The incidence of adverse events in patients in the Zovirax Duo groups differed between the Phase III studies, with a higher percentage of subjects reporting adverse events in the pivotal study than in the studies involving immunocompromised or adolescent patients.

In the combined Phase III studies, 'other herpes labialis recurrences', headache, nasopharyngitis, upper respiratory tract infection, and dry lip were the only events reported in $\geq 1\%$ subjects in any treatment group, and all occurred in a higher percentage of subjects in the vehicle group than in the Zovirax Duo group.

Adverse events in the paediatric study

During the paediatric study, MP 800, (N = 54), Zovirax Duo was well tolerated in children 6 through 11 years of age. Adverse events were minimal, and none were severe or serious. A total of 8 subjects reported adverse events, in 5 of these 8 subjects the Investigator evaluated the events are being not related to treatment with the study medication.

A total of 3 subjects with treatment related adverse events reported a total of 5 events. Two were specific to application site reactions including dryness, pain at the site, two included reports of pruritus and rash, and 1 subject reported oral paraesthesia.

In 2 of the 3 subjects with adverse events that were considered to be treatment-related, the events were mild or moderate, were specific to the application site, and led to treatment discontinuation for these subjects.

Table 2. Summary of exposure (all studies).

| Study | Study type | Population studied | Duration (days) | Number of subjects receiving at least one dose of treatment | | | | |
|---------------------|---|--------------------|-----------------|---|---------------------|---------------------|-------|---------------------|
| | | | | Zovirax Duo ^a | Zovirax Duo vehicle | ACV 5% ^b | HC 1% | ME609B ^c |
| 99-609-005 | Phase I, skin blanching <i>During first 24 hours, all 20 subjects had all three treatments 3 times per day.</i> <i>On days 2-7, specified number of subjects had treatments 5 times per day.</i> | Healthy | 1 | 20 | - | 20 | 20 | 20 |
| | | | 6 | 7 | | 20 | 6 | 7 |
| 604598 ^d | Phase I, skin irritation <i>Semi-occlusive patch applied to upper arm, once daily for 21 days</i> | Healthy | 21 | 36 | 36 | 36 | - | - |
| 604603 | Phase I, skin sensitization <i>Semi-occlusive patch applied to the back 3 times a week (for 48 hours on weekdays and 72 hours on weekends), for 3 weeks during induction phase. Followed by a 2-week rest prior and one challenge patch (48 hours) with 7 subjects re-challenged. *</i> | Healthy | See text * | 225 | 225 | | | |
| KGL6201 | Phase I, phototoxicity | Healthy | 1 | 30 | 30 | - | - | - |

| | | | | | | | | |
|------------|--|-----------------|------------|-----|-----|-----|---|---|
| | <i>Single dose application to back with semi-occlusive dressing, for 24 hours followed by ultraviolet irradiation.</i> | | | | | | | |
| KGL6202 | Phase I, photoallergy <i>Semi-occlusive patch applied to the back for 24 hours followed by ultraviolet irradiation, 2 times weekly for 3 weeks (6 times), 2-week rest, and challenge patch (24 hours) with 4 subjects re-challenged*</i> | Healthy | See text * | 50 | 50 | - | - | - |
| 98-609-013 | Phase II, (UV induced) <i>Application 6 times daily, 2 days after UV exposure, for a maximum of 5 days after start of lesion development*</i> | Herpes labialis | See text * | 190 | 190 | - | - | - |
| 609-04 | Phase III, pivotal study | Herpes labialis | 5 | 601 | 232 | 610 | - | - |
| 609-06 | Phase III, immunocompromised | Herpes labialis | 5 | 77 | - | 30 | - | - |
| 609-07 | Phase III, adolescents | Herpes labialis | 5 | 134 | - | - | - | - |
| MP 800 | Phase III, paediatric | Herpes labialis | 5 | 54 | - | - | - | - |

a. In Studies No. 99-609-005 (skin blanching) and No. 98-609-013 (UV induced), an unbuffered Zovirax Duo formulation (no citric acid) was used. In Studies No. 604598 (skin irritation), No. 604603 (skin sensitization), Zovirax Duo formulations were used with a slightly higher concentration of citric acid than in the final Zovirax Duo formulation.

b. Zovirax Cold Sore Cream was used in Study No. 99-609-005 (skin blanching) and Study No. 604598 (skin irritation) as aciclovir 5% cream, in the rest of the studies aciclovir 5% in the Zovirax Duo vehicle.

c. ME-609B – test formulation containing less isopropyl alcohol than ME-609 and was not progressed.

d. In Study No. 604598, 36 subjects also received both a positive (SDS) and a negative control (NaCl)

Table 3. Percentage of subjects reporting at least one adverse event in the Phase II and Phase III studies.

| Study No | Study description | Zovirax Duo | Aciclovir in vehicle ^a | Vehicle ^a |
|-----------|-------------------------------|-------------|-----------------------------------|----------------------|
| 90-609-13 | Phase II (UV-induced) | 65% | | 66% |
| 609-04 | Phase III (pivotal) | 18.5% | 16.4% | 19.4% |
| 609-06 | Phase III (immunocompromised) | 7.8% | 16.7% | |
| 609-07 | Phase III (adolescents) | 3.7% | | |

a Zovirax Duo vehicle

Skin atrophy

Skin atrophy may occur when products with stronger glucocorticoid activity than hydrocortisone are used for extended periods of time (months or years). In the skin blanching study and the Phase II study, skin atrophy was specifically evaluated by the investigators. There was no evidence of atrophy

in the skin blanching study. Only one patient had signs of atrophy in the Phase II study and this patient received placebo. No atrophy was reported in connection with Zovirax Duo treatment in the Phase III studies.

Local application site reactions

Local application site reactions have been examined in detail due to the topical route of administration of Zovirax Duo. In addition, these events account for most of the labelled undesirable effects of the marketed formulations of the individual active ingredients; the excipients account, at least in part, for some of the effects.

Local application site adverse events were reported more frequently in the Phase II study in which the recurrent herpes labialis recurrences were induced using ultraviolet radiation (UVR) than in the Phase III studies where the lesions were not induced and allowed to recur naturally. The UVR may have been responsible for at least some of the local adverse events in the Phase II study. In particular, the sunburn caused by the UVR was coded as 'photosensitivity reaction'. Local application site adverse events for the Phase III studies (combined) are given in Table 4.

Table 4. Subjects with topical treatment adverse events for the Phase III studies combined.

| WHO Preferred Term | Zovirax Duo N = 812 | Aciclovir in vehicle^a N = 640 | Vehicle N = 232 |
|---|--------------------------------|---|----------------------------|
| Number of subjects who had at least one topical reaction adverse event | 32 (3.9%) | 21 (3.3%) | 11 (4.7%) |
| Application site dryness [n (%)] | 4 (0.5%) | 4 (0.6%) | 3 (1.3%) |
| Application site irritation [n (%)] | 4 (0.5%) | 4 (0.6%) | 0 (0.0%) |
| Application site erythema [n (%)] | 1 (0.1%) | 3 (0.5%) | 0 (0.0%) |
| Application site anaesthesia [n (%)] | 0 (0.0%) | 2 (0.3%) | 1 (0.4%) |
| Application site paraesthesia [n (%)] | 2 (0.2%) | 1 (0.2%) | 0 (0.0%) |
| Application site exfoliation [n (%)] | 2 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| Application site pain [n (%)] | 0 (0.0%) | 1 (0.2%) | 1 (0.4%) |
| Application site discoloration [n (%)] | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Application site scar [n (%)] | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Application site hypersensitivity [n (%)] | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Application site inflammation [n (%)] | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Lip dry [n (%)] | 8 (1.0%) | 2 (0.3%) | 3 (1.3%) |
| Chapped lips [n (%)] | 3 (0.4%) | 3 (0.5%) | 1 (0.4%) |
| Cheilitis [n (%)] | 3 (0.4%) | 0 (0.0%) | 1 (0.4%) |
| Hypoaesthesia oral [n (%)] | 0 (0.0%) | 1 (0.2%) | 1 (0.4%) |
| Lip pain [n (%)] | 0 (0.0%) | 1 (0.2%) | 1 (0.4%) |
| Lip disorder [n (%)] | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Oral discomfort [n (%)] | 0 (0.0%) | 0 (0.0%) | 1 (0.4%) |
| Paraesthesia oral [n (%)] | 0 (0.0%) | 0 (0.0%) | 1 (0.4%) |

| | | | |
|------------------------------------|----------|----------|----------|
| Dysgeusia [n (%)] | 3 (0.4%) | 0 (0.0%) | 0 (0.0%) |
| Swelling face ^b [n (%)] | 1 (0.1%) | 0 (0.0%) | 1 (0.4%) |
| Erythema [n (%)] | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |

a: Zovirax Duo vehicle

b: Reported term/verbatim was “swelling upper lip”. Mapped as PT swelling face.

n: Number of subjects

N: Total subjects

Post-marketing safety data

The sponsor employs a routine, pro-active process for identifying safety signals with three main components:

- a) ongoing awareness and review of important individual cases, including all reports with a fatal outcome,
- b) systematic, regular and proactive review of aggregate safety data, and
- c) systematic, regular review of the literature.

A holistic approach is used so that all relevant data sources are interrogated when evaluating safety signals (e.g. external sources, clinical studies, epidemiological studies, pre-clinical information). All signals identified are evaluated and, following evaluation of the signal, appropriate action is agreed. The options include continuing routine proactive pharmacovigilance, defining further work to better understand the risk, or recommendation of a label change. Through the use of this process, issues of potential concern are promptly detected and, where appropriate, communicated expeditiously to regulators and regulatory authorities.

A full copy of the most recent Periodic Benefit Risk Evaluation Report (PBRER) is provided in Appendix 1 of this application, relevant details with respect to toxicity and safety are summarised below.

Post-marketing experience with individual active ingredients

Whilst the post-marketing experience for the combination Zovirax Duo product is presently limited to 7 years, there is extensive post marketing experience with aciclovir cream based on use for over 30 years.

Aciclovir alone has a long-established safety and efficacy profile and a large exposed population. Exposure for topical aciclovir is extensive. As of June 2016, assuming one tube represents one treatment course, it was estimated that there have been approximately:

- 403 million patient exposures to non-prescription cold sore cream, and
- 897 million treatment courses of aciclovir ointment and cream (prescription).

Aciclovir cream is generally well tolerated. Most adverse events associated with its use are mild and transient in nature. With aciclovir cream, these events are generally limited to local application site reactions such as uncommon transient burning or stinging, mild drying or flaking of the skin, itching, and rarely erythema or contact dermatitis. Immediate hypersensitivity reactions are very rare.

There is also extensive experience with hydrocortisone alone. Hydrocortisone is widely available without a prescription for a wide range of inflammatory conditions. The benign safety profile of

topical hydrocortisone is reflected in its availability for non-prescription use in strengths of 1% and 0.5% in many countries.⁴⁵

The strength and route of administration of hydrocortisone in Zovirax Duo is the same as in hydrocortisone 1% cream. However, although Zovirax Duo is applied five times daily, hydrocortisone 1% cream is usually applied two to three times a day. This does not present a potential problem of overdosage of hydrocortisone because the total dose of the active ingredient in Zovirax Duo is less than that available in the maximum pack size of hydrocortisone 1% cream available without prescription.

Topical 1% hydrocortisone products:

- are effective in reducing itching and inflammation associated with skin disorders and rashes
- have been approved for decades for these pruritic and inflammatory indications
- are available without prescription in packs up to 30 g.

Hydrocortisone 1% has already been successfully combined with anti-infective agents in several topical products, including creams and ointments as well as ophthalmic and otic suspensions. Products for dermal use which combine hydrocortisone 1% with miconazole (e.g. Resolve Plus) or clotrimazole (e.g. Canesten Extra) are available and well-established in New Zealand as Restricted Medicines.

The 1% hydrocortisone concentration in Zovirax Duo was selected based on the established safety and efficacy of this concentration in topical products. Adequate clinical data are available to support the safety and efficacy of Zovirax Duo for the treatment of recurrent herpes labialis episodes in adults and adolescents (aged 12 years and older) when applied five times daily for 5 days.

Adverse event reports with Zovirax Duo

As of 31st July 2016, 30 adverse event reports have been received after exposure to the product from prescription and non-prescription sources. The 30 cases, containing 70 adverse events, were classed as non-serious.

Characterisation of identified risks

Zovirax Duo is administered via the topical route and the adverse reaction profile comprises skin application site reactions and contact dermatitis. Based on clinical trial data with the combination product and post-marketing experience with topical aciclovir (alone) most of the local application site events are non-serious and occur commonly or uncommonly (drying or flaking skin, transient burning or tingling) and/or rarely (erythema, pigmentation changes and signs and symptoms of inflammation at the application site).

Cases of contact dermatitis in the Zovirax Duo clinical studies were non-serious, and resolved following discontinuation of treatment; none of the reactions spread beyond the site of application or had any systemic involvement. The incidence of contact dermatitis or contact sensitisation is higher when topical products are applied using occlusive patches, as is the practice when performing dermal safety studies.

Hypersensitivity reactions including angioedema have been observed with single active topical aciclovir and based on post-marketing data are very rare; they have not yet been observed with the Zovirax Duo combination product.

In Summary:

- Local skin reactions are established labelled events which do not require further characterisation or evaluation, and for which routine pharmacovigilance is sufficient.
- Contact dermatitis in association with aciclovir is rare and predominantly non-serious. However, in rare cases epidermal contact with an allergen results in a hypersensitivity reaction causing anaphylactic shock, which if untreated, can be fatal. Contact dermatitis has been identified as an important potential risk and the appropriate risk mitigation is considered to be adequate label warnings (See PBRER, Section 16.4.1; provided in Appendix 1 of this application).

Assessment of benefit:risk profile

The benefit:risk profile of Zovirax Duo for use in immunocompetent adults and adolescents (12 years of age and older) for the treatment of recurrent herpes labialis is favourable. During the period under review, no actions have been taken or proposed for safety reasons. There have been no amendments to the sponsor's Reference Safety Information (RSI) in the current reporting period and no further amendments to the RSI are considered necessary at this time.

Based on the information provided in this report, there has been no change to the benefit:risk balance of Zovirax Duo.

B10. Potential for abuse or misuse

The proposed Data Sheet and associated CMI/carton for Zovirax Duo clearly state that the product is indicated for use on cold sores, with warnings that the product is only to be used on the lips and face and that it should not be used to treat genital herpes or used in the eye. The proposed Data Sheet and associated CMI/carton also clearly state that Zovirax Duo is indicated for adults and adolescents aged 12 years of age and older, and that the product is not to be used in children under 12 years.

The most important potential risk for non-prescription Zovirax Duo is off label or inappropriate use. Based on the nature of the condition being treated, the small pack size, and the limited potential for systemic exposure (given the low dosage and localised application, and the low potency of hydrocortisone), any off-label/inappropriate use would be highly unlikely to give rise to safety issues.

A framework for the systematic assessment of the benefits and risks relevant to non-prescription drugs has been proposed.⁴⁶ The risk domains have been examined in detail for Zovirax Duo and are summarised below.

Unintended misuse

RHL is very common, and this fact alone makes it a readily recognisable condition. RHL is an established and easily identified indication for self-assessment. The prodromal symptoms that often herald an episode of RHL and the distinct appearance and typical location of recurrences on the lips or around the lip margins, reduce the risk that the condition would be mistaken for other dermatological conditions on the face.

Self-treatment of RHL with general sale aciclovir 5% w/w has been possible in New Zealand for 15 years. Importantly, the characteristic signs and symptoms associated with the early stages of a cold sore are recognised by many sufferers, and so can prompt early intervention with Zovirax Duo, which is critical to maximise the likelihood of preventing the development of ulcerative lesions.

If the product were used to treat a non-HSV skin lesion, it would not be expected to lead to serious consequences (mainly due to low systemic absorption, limited duration of use and application to a relatively small area of skin). Experience with topical aciclovir 5% cream has not identified any significant issues with application to an inappropriate site.

Intentional misuse with therapeutic intent

In many countries, aciclovir cream is indicated for RHL only. The extent of off-label usage with these products is unknown; however, no specific safety issues have been identified in relation to off-label usage.

There is the potential for off-label usage by subjects with recurrent genital herpes. Experience with topical aciclovir 5% cream has not identified any significant issues with application to an inappropriate site. The small 2 g pack size for Zovirax Duo and small aperture nozzle make use over widespread areas such as genitals unlikely. RHL can occur in children, with most infected between 6 months and 14 years of age, and typically before 5 years of age. Although the efficacy of Zovirax Duo in children has not been investigated, Zovirax Duo Cream was safe and well tolerated when used for the treatment of herpes labialis recurrences in immunocompetent children aged 6 to 11 years, following a 5-day treatment with 5 times daily topical application.

Topical aciclovir is not recommended in immunocompromised subjects as recurrent HSV infections in this population may become severe and widespread, with systemic involvement, and therefore require systemic antiviral therapy. Use in immunocompromised patients is considered unlikely given clear labelling warning against such use. These patients require the on-going care of a physician. In the event of misuse in this setting, the risk would appear to be no different than for topical aciclovir cream which is currently unscheduled. Long term use (>5 days) is considered unlikely based on pack presentation, and associated effects are considered unlikely based on the limited systemic absorption of the active ingredients.

Zovirax Duo has not been studied in patients with concomitant dermatitis of other origin. The proposed package leaflet (consumer medicines information, CMI) will provide clear direction to the patient on the condition for which Zovirax Duo is appropriate. The small pack size (2 g) and clear guidance on duration of use (5 days) substantially limit the potential for Zovirax Duo to be used to manage dermatitis.

Accidental ingestion

Topical application or accidental ingestion of the whole 2 g tube of Zovirax Duo is unlikely to lead to adverse effects. If the full contents were to be swallowed, the ingested amount of aciclovir (100 mg) is half that contained in a single aciclovir 200 mg tablet.

By comparison, oral doses of 800 mg aciclovir five times a day (equivalent to 4 g per day) for 7 days are used for treatment of herpes zoster. Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects.

Similarly, if the entire contents of a 2 g tube of Zovirax Duo were to be taken orally, the amount of hydrocortisone ingested being 20 mg, the resulting plasma levels of hydrocortisone would be well below endogenous levels.

Intentional overdose

See paragraph above, Accidental ingestion.

Worsened outcome due to self-management:

There is limited opportunity for mistaken self-diagnosis. Although there are other potential orofacial lesions (including those resulting from bacterial and fungal infections), they are unlikely to be confused with RHL (see section B3).

The use of Zovirax Duo does not present a risk of masking serious disease if applied in cases of misdiagnosis of the skin lesions. Aciclovir cream and hydrocortisone cream individually are both well tolerated, even if applied to damaged skin. There is a theoretical risk that hydrocortisone cream could exacerbate local bacterial or fungal skin infections such as acne, boils, impetigo or thrush. However, as subjects with RHL in most cases recognise the signs and symptoms of an emerging episode, this risk is extremely low.

Masking symptoms or delaying diagnosis of a more serious condition has not been an issue for aciclovir 5% cream, which has been available for use without prescription in New Zealand for 15 years. Zovirax Duo will be used for the same indications and thus it is unlikely to present a problem, particularly given supply under the supervision of a Pharmacist.

Whilst there is a low potential for abuse or misuse, the mitigation of any potential risk mitigation will be achieved through the safety messages in the packaging and CMI and the involvement of the Pharmacist at the point of purchase. The involvement of a Pharmacist in the sale of the product is appropriate; it will enhance the provision of usage information to the consumer and will also serve as a means for monitoring any risks.

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