PART A

1. International non-proprietary name (INN) and British approved name (BAN) of the medicine.

Aciclovir (USAN), acycloguanosine, aciclovirum, BW-248U
Chemical name: 9-[2-hydroxyethoxy)methyl]-9H-guanine; 2-amino-1,9-dihydro-9-[(2-hydroxy-ethoxy)methyl]-6H-purin-6-one

2. Trade name.

ZOVIRAX™ Cold Sore Cream

3. Company requesting reclassification.

GlaxoWellcome (NZ) Ltd
Eighth Floor, Quay Tower
cnr Customs & Albert Streets
PO Box 106
Downtown, Auckland
NEW ZEALAND

4. Dose form and strength.

Zovirax™ Cream is a smooth, white to off-white cream containing 5% w/w of Aciclovir.

5. Pack size and other qualifications.

ZOVIRAX Cold Sore Cream contains aciclovir 50mg/g in packs of 2 g.

Zovirax ™ Cream is currently sold as a PHARMACY MEDICINE. It is indicated for use by adults and children and has a 5 times daily application regime.

6. Indication for which change sought.

Zovirax ™ Cold Sore Cream is indicated for the topical treatment of *Herpes simplex* virus infections of the lips and face. ZOVIRAX Cold Sore Cream contains aciclovir 5%w/w and is intended for short term self-treatment (5 days) of cold sores.

7. Present classification of medicine.

Pharmacy Medicine

8. Classification sought.

General Sale Medicine

9. Classification in other countries where marketed.

ZOVIRAX Cream was first approved 15 years ago in many countries and has been an OTC product in countries such as UK, Germany, Australia, Belgium, Denmark, Ireland, and Switzerland for more than five years. During this time in excess of 200 million packs of this product have been sold.

Australia- In 2001 November an application to reclassify aciclovir to an unscheduled product was considered by the NDPSC. The committee

recommended that aciclovir 5%w/w cream when used for treatment of cold sore should be exempted from scheduling. (Appendix 4)

10. Extent and duration of usage.

Aciclovir 5%w/w cream was first registered in New Zealand in 1984. It has been available as Pharmacy Medicine in New Zealand under the tradename ZOVIRAX™ Cream since 1992.

11. Proposed labelling.

Draft primary and secondary container labelling for the reclassified presentation of ZOVIRAX™ Cold Sore Cream is contained in Appendix 2.

12. Proposed warning statements.

Following statements are proposed for the reclassified product:

TUBE LABEL:

-For external use only.
-Safety sealed. Do not use if the sealed nozzle is punctured.
-Do not refrigerates.
-Keep all medicines out of the reach of children.
-Always read the enclosed leaflet.

CARTON LABEL:

-For external use only.
-Do not use in eyes.
-If symptoms persist consult your doctor.
-Do not use if you are pregnant unless your doctor advises you.
-Do not refrigerate.

PACKAGE LEAFLET:

The package leaflet contains a significant body of information under the following headings. (Appendix1)

- How does ZOVIRAX work

- Is ZOVIRAX Cold Sore Cream suitable for me
- How to use ZOVIRAX Cream
- Some Do's And Don't's
- What unwanted effects does ZOVIRAX Cold Sore Cream cause
- Overdose
- Where do I keep ZOVIRAX Cold Sore Cream
- Other information- what is a cold sore, when does it occur
- What does ZOVIRAX Cold Sore Cream look like
- What does ZOVIRAX Cold Sore Cream contain

13. Other products containing the same active ingredient, which may be affected by the proposed classification, change.

Other products containing aciclovir an active for the treatment of cold sores are

- Lovir (Douglas), Cream, 2g
- Viraban (AFT), Ointment, 3g
- Zolaten (Pharmaco), cream, 2g

Part B - Reasons for requesting classification change.

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

This application seeks to have ZOVIRAX (aciclovir) Cold Sore Cream, which is currently a PHARMACY MEDICINE to be reclassified as an unscheduled medicine (GENERAL SALES MEDICINE) when sold in a small pack size of 2g.

ZOVIRAX Cold Sore Cream is indicated for the treatment of *Herpes simplex* virus infections of the lips (herpes labialis).

1.1 PROBLEM STATEMENT

It is estimated that 20 to 40% of the normal population suffer, at some stage in their life, from cold sores. Many individuals experience only one to three episodes per year, but some can have 12 or more attacks a year (4). Typically an untreated episode will last eight to ten days, but can continue for up to 14 days (5). Approximately 93% of all sufferers treat their cold sores (data on file).

Recurrent cold sores are usually mild and self-limiting, however the unsightly blisters caused by the cold sore virus can be a considerable problem for some people. Many sufferers are physically and emotionally distressed during an attack

1.2 TREATMENT

Clinical studies have shown that early use of ZOVIRAX Cold Sore Cream can prevent the cold sore. Dermatological conditions can be unsightly, embarrassing and emotional for some people. Many products, which are currently available, are only palliative in nature. Wider availability of effective cold sore products to enable treatment of this condition can only be considered as a benefit for the consumer.

In New Zealand, a number of preparations are available for treatment of *herpes labialis*. They can be categorised into two sections.

Symptomatic or palliative treatment

Topical antiviral

1.2.1 symptomatic or palliative treatment

Over the years a wide variety of substances have been used to relieve the symptoms of cold sores and prevent secondary bacterial infection. The remedies, which have either been used alone or in combination include:

- Astringents and antiseptics e.g. povidone- iodine, benzalkonium chloride, phenol
- Softening and hydrating agents e.g cream base, glycerine
- Local anaesthetics e.g. lignocaine, benzocaine
- Oral analgesics and anti-inflammatory e.g. paracetamol and aspirin

These do not alter the natural history of the viral infection; rather they offer only relief of discomfort and pain and available in both Pharmacy and non pharmacy outlets.

1.2.2 Topical antiviral

Aside from Aciclovir, there are currently only two types of antiviral topical creams available in New Zealand for the treatment of *herpes labialis.* They are idoxuridine (Stoxil- discontinued in NZ), idoxuridine and lignocaine (Virasolve) and penciclovir (Vectavir). It is important to note that while idoxuridine containing products are classified as general sales medicine.

1.3 ACCESS

Good medical practice for any viral infection is to treat the disease early during the stage of viral replication. Treatment of cold sores with aciclovir is most effective when it is initiated early, preferably during the prodromal stage of pain, tingling

itching and erythema. Clinical data show treatment with aciclovir cream initiated early in the course of an infection (ie, before the damage phase is complete), is expected to shorten the time to onset of the ulcer or crust stage, as well as reduce the total healing time by a third. It also halves the duration of symptoms. (15) As this is a recurrent disease most patients will be able to recognise these symptoms and initiate treatment. For early treatment to occur easy access is an absolute prerequisite.

As a Pharmacy Medicine aciclovir cream is theoretically easily available, however access is restricted to retail pharmacies. An unscheduled listing will increase the number of outlets by over 60% to generally improve consumer access. In New Zealand all coldsore preparation whether they are palliatives or antiviral treatments are all sold in pharmacies only.

In light of the importance of increased access it is worth noting that the MCC has previously considered that the availability of a topical antiviral cream for coldsores as an unscheduled product was beneficial to public health. Accordingly in 1998 they descheduled idoxuridine for the treatment of coldsores.

However, idoxuridine now has been withdrawn from the marketplace. Idoxuridine with lignocaine preparations are only available in pharmacies despite the fact the classification of the product is general sales. This leaves the public with no other antiviral products with an easy access. Therefore the proposed change of aciclovir for the treatment of coldsores would restore wider patient accessibility to a product proven to have benefits for the sufferer.

2. Ease of self-diagnosis for the condition indicated

ZOVIRAX Cold Sore Cream is indicated for the treatment of *Herpes simplex* virus infections of the lips. Recurrent cold sore suffers are very familiar with their condition and can easily recognise the signs and symptoms of a new lesion developing.

Knowledge of cold sores is so wide spread that the possibility of the misdiagnosis is

almost non existent. The earliest symptoms of the cold sore are easily identifiable, and the majority of sufferers self diagnose and treat. These may have included products containing idoxuridine, povidone iodine, menthol or camphor, which are available, as non-scheduled (General Sales Medicine) products.

In practice 20% of sufferer's use palliative treatments, which have no effect on the cause of the diseases, rather they offer relief for discomfort and pain. The other 80% seek antiviral treatment, which needs to be promptly self initiated to maximise the effect of treatment and potential benefit to sufferers.

GlaxoSmithKline believe that ZOVIRAX Cold Sore Cream when used as directed is suitable for self-treatment of the afore-mentioned ailment and capable of being monitored by the consumer. Lesion formation and resolution follows a well established self limiting path and so sufferers are able to monitor the progression of their condition. Owing to the short dosing period and small pack size (2g) any delay in correct diagnosis would be unlikely to affect the prognosis.

3. Relevant comparative data for like compounds.

Similar antiviral treatment such as Idoxuridine, and idoxuridine and lignocaine are currently classified as general sales medicine in New Zealand.

4. Local data or special considerations relating to NZ

Local data has been supplied in the specific sections throughout this submission. No additional local data has been supplied in this section. (Appendix 3)

5. Interactions with other medicines

No known interactions.

6. Contraindications

ZOVIRAX Cold Sore Cream is contra-indicated in patients known to be hypersensitive to aciclovir, or any other constituents of the cream. Contraindications and precautions are consistent with those for products containing idoxuridine, idoxuridine and lignocaine, povidone iodine, which are available, as non-scheduled products for cold sore treatments.

7. Possible resistance

The possibility of development of resistance to aciclovir, particularly for HSV-1 and HSV-2, has been constantly monitored by Glaxo Wellcome over the past 18-20 years. Surveillance studies to isolate, identify and characterise resistant mutants were started before the first worldwide launch of aciclovir in the early 1980s [18, 19]. The following is a general summary of the information available from this programme with a more detailed description of a recent study.

Early laboratory studies first identified resistant variants of HSV and these were then studied extensively. Resistance arises from mutations in the genes coding for one or other of the viral enzymes involved in the mechanism of action of aciclovir:thymidine kinase (TK) or DNA polymerase. The majority of resistant viruses fail to express TK. This defect is also associated with a dramatic attenuation of virulence and a failure to reactivate from latency. More subtle mutations, associated with changes in substrate specificity of one or other of the enzymes, show only slight attenuation compared with wild-type virus but occur much less frequently.

This potential for resistance to aciclovir led Glaxo Wellcome to establish an extensive programme of resistance monitoring based in the UK and USA. On a worldwide basis around 5000 clinical isolates were collected between 1979 and 1993 by

Glaxo Wellcome, and their susceptibility to aciclovir determined. The nature of the resistance appears to mirror that found in the laboratory: the most common genotype seen was a TK deficient virus, with substrate specificity mutants only seen rarely. Since the isolates tested are generally not randomly selected, it is difficult to determine the frequency with which resistance develops.

In severely immunocompromised patients (e.g. HIV patients or bone marrow transplant recipients) it is probably in the range of 5% and can be associated with clinical resistance. In the immunocompetent, it appears that resistance develops extremely rarely and there is no well-documented case of treatment failure due to resistance. Evidence for the low potential for emergence of viral resistance with topical aciclovir includes an analysis on 263 isolates from 116 topically-treated, immunocompetent patients. Seven (2.7%) of these isolates were found to be resistant to aciclovir but this did not differ significantly from the baseline prevalence of resistant isolates found prior to the introduction of aciclovir. The rare occurrence of resistance together with the reduced virulence of TK deficient mutants makes the transmission of resistant virus highly improbable [20].

More recently a surveillance study was conducted in the UK where Zovirax Cold Sore Cream had been available OTC for five years. A total of 923 isolates were obtained from 1297 patients with herpes labialis, and of these 751 were tested for aciclovir susceptibility. Only one isolate (0.1%) was found to be resistant to aciclovir [21]. Thus the widespread availability of OTC Zovirax Cold Sore Cream has not led to an increase in resistance to HSV.

In summary, availability of Zovirax Cold Sore Cream as a general sales medicine for use in immunocompetent individuals is unlikely to pose a risk to the individual or the community due to development of viral resistance.

8. Adverse events - nature, frequency etc.

The most common adverse event reported is flaking skin with less frequent reports of dry skin, burning or stinging. All these events were considered minor and no patient stopped therapy because of adverse events.

Erythema and itching have been reported in a small proportion of patients. Contact dermatitis has been reported rarely following application. Where such sensitivity was observed, tests have indicated the cause to be components of the cream base rather than aciclovir. (See appendix 3 and volume 2)

In New Zealand from 1983 – 1990 aciclovir was monitored under IMMP. In New Zealand approximately 1.2 million units of Zovirax alone were sold between the period on 1996-2001. There have been only 7 cases reported in New Zealand to CARM (see attached report- appendix3) highlighting the safety of the product.

SUMMARY OF GLOBAL ANALYSIS OF ADVERSE EVENTS

- ZOVIRAX Cold Sore Cream is generally well tolerated for the treatment of HSV infections of the lips and face.
- An extensive database has revealed that adverse reactions are essentially limited to dryness or flaking of the skin or lips and other occasional application-site events.
- Overall, adverse events were no different for ZOVIRAX Cold Sore Cream or the vehicle control indicating that such experiences were either naturally occurring (e.g. headaches, respiratory infections) or resulted from the vehicle itself (e.g. skin and application-site events).
- Although approximately 10% of patients in clinical trials reported adverse events, no more than 5% were considered possibly related to study drug. Of these latter events, only 2% were reported as dryness or flaking of the skin and 1% were local application-site reactions.
- More than 200 million patient exposures to ZOVIRAX Cold Sore Cream have been estimated to have occurred with a very low reported spontaneous adverse event rate (<0.001%).

9. Potential for abuse or misuse.

9.1 Extremely low abuse potential

Abuse potential is low due to minimal systemic absorption.

9.2 Low potential for harm from inappropriate use

Cold sores are self-limiting condition, with most lesions progressing to ulcer or crust stage within 48 hours. Healing is generally complete with in 8-10 days. It is known that 25% of lesions spontaneously abort at prodrome stage. In these cases the use of aciclovir is minimised, thus eliminating any inappropriate excess use of the product.

The proposed small pack size of 2g would make inappropriate use for conditions such as genital herpes both inconvenient and costly. In addition an amount of 2g would be insufficient for treatment of genital herpes.

Appropriate instructions contained in the pack insert will direct consumers towards proper use. The information carries an instruction that the cream should be used only for cold sores on the mouth and perioral areas. Finally the product name will reinforce that it should be used for treatment of cold sores.

9.3 Overdose

Topical application of the whole tube would not lead to any adverse effects. Even if the whole content of a tube were to be swallowed there would be no risk to patients.

The amount of aciclovir in the whole 2g tube is less than that in a 200mg tablet. Oral doses of 800mg aciclovir five times a day (4 grams per day) have been administered for 7 days without adverse effects. Single intravenous doses of up to 80mg/kg have been inadvertently administered without adverse effects.

No other toxic effects are likely from the other components of the cream. Aciclovir can be removed from the circulation by haemodialysis.

9.4. Risk of Mistreatment

The likelihood of misdiagnosing of recurrent *herpes labialis* is extremely low, as the lesions are very distinct and the sufferers and the general community are well educated in this regard. This has been clearly established as the product was launched as an OTC medicine since 1993. Cold sores are generally non serious (and self limiting) and failure to treat will not cause major health issues.

Conversely as ZOVIRAX cream is well tolerated, even to damaged skin, misapplication to other peri oral lesions would not be expected to aggravate or mask symptoms, or to adversely affect the systemic profile. In the rare event of confusion with acne, boils, insect bites, the use of ZOVIRAX cream would not be expected to lead to serious consequence. Therefore the use of ZOVIRAX Cold Sore Cream does not present a risk of masking serious disease.

9.5 Low risk of complicating the medical management of a disease

The use of ZOVIRAX Cold Sore Cream does not present a risk of complicating the medical management of a disease.

Herpes labialis is a common self-limiting disease which patients are able to diagnose themselves and is highly amenable to self-treatment. Little or no pharmacy assistance is required in selection of product due to the self-diagnosable and self-medicable nature of the indication. The registered indication is able to be self diagnosed and the condition is generally self managed by the patient. It has been an established OTC indication since 1993 in the New Zealand market. Due to its self limiting nature, mismanagement is minimal.

Pivotal clinical trials (data on file) have clearly demonstrated that ZOVIRAX Cold Sore Cream reduces the duration of episodes of herpes labialis, the vesicle healing time and the duration of pain.

Extensive clinical trial and post-marketing data confirm that ZOVIRAX Cream is a safe and well tolerated treatment. There is a low rate of adverse events, which have been clearly identified, are generally mild and transient, and do not require withdrawal of treatment.

10. Conclusions

Herpes labialis is a common, self limiting disease. Although it is often considered rather trivial medically, it causes significant distress to many sufferers. There is a clear public need for effective and easily available topical antiviral products for the treatment of cold sores. It has been clearly demonstrated that the treatment of cold sores should be initiated as early as possible to maximise the benefit to the individual

Sufferers are clearly able to diagnose an attack themselves. The vast majority can recognise prodromal symptoms, (such as tingle and redness) and become aware of specific factors, which trigger an attack. This allows the sufferer to treat the cold sore at the prodromal stage, which reduces the episode time.
to make an accurate self-assessment of their condition.

The potential hazard from misdiagnosis is minimal. Due to the self limiting nature of the condition, it requires a limited duration of treatment, thus minimising the potential for over usage of the treatment.

Added safety assurance is afforded by

- the targeted application to the lesion
- the specificity of aciclovir for infected cells only
- often lengthy remission period of lesions and

the 20-year post marketing experience of the active aciclovir.

Most alternative products used for cold sores are at best providing palliative relief of the symptoms. The only alternative anti-viral treatment, available in the market is idoxuridine, which has been descheduled .

ZOVIRAX Cold Sore Cream is suitable for self-selection and self-treatment by the consumer. Descheduling would bring the product in line with currently available antiviral products for recurrent cold sores.