SUBMISSION FOR

RECLASSIFICATION OF MEDICINE

FAMVIR
(FAMCICLOVIR for *Herpes labialis)*
TT50-5457B

November 2008

Novartis New Zealand Limited
6-8 Mackelvie Street
Grey Lynn
AUCKLAND

SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING CHANGE

Novartis New Zealand Limited is seeking consideration of rescheduling of oral famciclovir for the treatment of *Herpes labialis* (cold sores) in immunocompetent patients from Prescription Medicine to Pharmacist Only Medicine.

OVERVIEW

Herpes simplex virus type 1 infects at least 265,000 New Zealanders with as many as 18 % of all adults aged 18 or older suffering from *Herpes labialis* (cold sores) at least every 2 years. In this group 20 % of 18 to 24 year olds suffer a cold sore annually.

Cold sores develop most commonly on or adjacent to the lips although occasionally they can occur on the nostrils, the chin or in the mouth. The mean duration of untreated classic (vesicular) lesions in recent placebo-controlled trials was between 5 and 6 days although this can be variable up to 20 days.

Herpes labialis (cold sores) is a short term and self-limiting condition, appropriate for self-diagnosis and management by consumers (*NDPSC Record of Reasons of Meeting 43 – February 2005*, page 6, viz: *The Committee agreed to exempt preparations (etc)…… on the grounds that Herpes labialis was a short term and self-limiting condition, appropriate for self-diagnosis and management by consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.)*

Most episodes of cold sores are mild, although significant irritation, pain discomfort and loss of self-esteem have been reported.

Treatment should be initiated as early as possible after the start of a cold sore infection, as viral replication is most active in the prodromal period or within the first 8 hours after lesion onset. The maximal frequency of virus-positive lesions occurs in the first 48 hours. The window of opportunity therefore for providing clinical benefit is during the early and brief period of time that viral replication dominates over the rapidly developing host immune response i.e. within the first 4 hours.

The availability of oral antiviral medication for the patient to self medicate within the first few hours of prodromal symptoms onset would achieve maximum possible suppression of viral replication.

A dose of 1500 mg famciclovir in a single day taken shortly after the onset of prodromal symptoms healed *Herpes labialis* lesions 2 days faster than placebo [Spruance 2006].

An acceptable safety and toxicity profile has been demonstrated for a 1500 mg single dose regimen.

For the three years covering 2004 to 2006, there were over 10.6 million person years of treatment globally. Famciclovir has been well tolerated in clinical trials with the most frequently reported adverse events being headache, fatigue and nausea. These were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment.

When used within 24 - 48 hours of an outbreak of *Herpes labialis*, famciclovir provides significantly faster healing of a cold sore lesion than placebo, suppression of viral replication and a reduction in the frequency of secondary cold sore lesions.

The extensive use of nucleoside analogues for the antiviral treatment of herpes infections for over 20 years has not been associated with an increased emergence of drug-resistant virus in immunocompetent or immuno-compromised patients [Bacon 2003]. Given that this submission for famciclovir proposes a single day therapy and not a chronic suppressive therapy, viral resistance is not considered to be an issue.

In light of substantial clinical experience and a favourable risk-benefit profile, Famvir (famciclovir) is a suitable candidate for re-scheduling to a Restricted Medicine at the proposed dose for cold sores in immunocompetent patients.

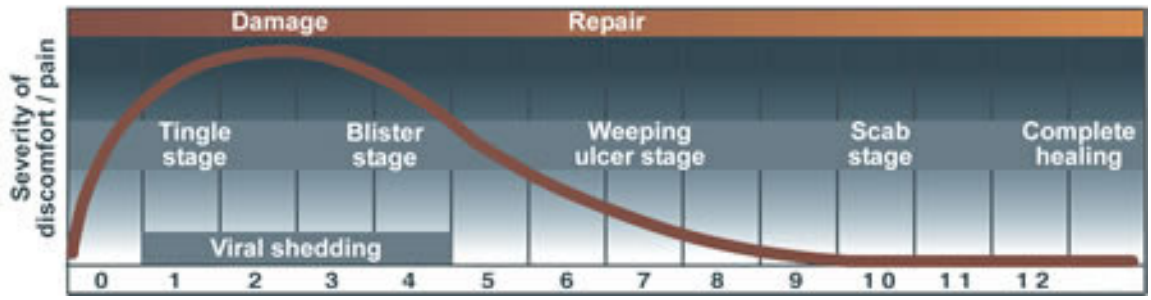
BACKGROUND

Famciclovir is a prodrug of the antiviral agent penciclovir. Following oral administration it is rapidly converted *in vivo* to penciclovir, which has demonstrable *in vitro* activity against herpes simplex viruses (HSV types 1 and 2) and *varicella zoster* virus (VZV). The antiviral effect of orally administered famciclovir is due to its in vivo conversion to penciclovir.

Cold sores usually develop and progress as indicated in Figure 1:

- Localised itching and tingling a day or two before the cold sore appears.
- A collection of small painful fluid-filled blisters form.
- Accompanying pain, tenderness, and sensation of heat and burning.
- Blisters burst after a few days creating weeping 'ulcer-like' sores.
- The blister site dries up and forms a scab or crust which can be itchy and painful.
- The crust dries up and eventually falls off after about 10-11 days without leaving a scar.

Figure 1: Phases of a cold sore [adapted from Spruance 1995]



By commencing treatment for cold sores during the tingling phase, Famvir® can provide significantly faster healing of the lesion, suppression of viral replication and a reduction in the frequency of secondary cold sore lesions.

Current regulatory status

The first worldwide registration of famciclovir occurred in Great Britain in 1993, and is currently marketed by Novartis in over 69 countries. Famciclovir 125, 250mg tablets were registered in New Zealand in November 1994 and the 500mg was registered in December 1998. Famciclovir is marketed under the name "Famvir®". Famvir® is not currently marketed in New Zealand.

In November 2007, FAMVIR® (famciclovir) was approved for the treatment of recurrent *Herpes labialis* (cold sores) in New Zealand at a total dose of 1500 mg administered as a single dose. To accommodate this indication, a pack of 3 x 500 mg tablets was designed specifically for the treatment of cold sores.

Novartis proposes that this single treatment famciclovir pack when labelled for the treatment of *Herpes labialis* in immunocompetent patients **only** be re-classified to Restricted Medicine. All other famciclovir indications and dosage regimens will retain their current Prescription Medicine classification.

PART A – PRODUCT SUMMARY

1. **International non-proprietary name**
   Famciclovir

2. **Proprietary name**
   Famvir (TT50-5457b)

3. **Company requesting reclassification**
   Novartis New Zealand Limited
   6 – 8 MacKelvie Street,
   Grey Lynn,
   AUCKLAND

4. **Dose forms and strengths for which a reclassification is sought**
   Tablets – 500mg

5. **Pack size and other qualifications**
   3 tablet blister pack

6. **Indications for which change is sought**
   For the treatment of recurrent herpes labialis (cold sores).

7. **Present classification of medicine**
   Prescription Medicine

8. **Classification sought**

   Restricted Medicine classification for the following indication only:
   - Famvir is indicated for the treatment of recurrent herpes labialis (cold sores) supplied in packs containing no more than 3 tablets with a maximum one off dose of 1500mg.

   All other strengths, dosage and usage to remain Prescription Medicine

9. **Classification status in other countries:**
   Reclassification submission for this strength and indication was submitted in Australia in September 2008.
   USA - Herpes labialis (cold sore) indication - Prescription Medicine

10. **Extent of usage in NZ and elsewhere:**
    NZ usage: FAMVIR has not been marketed in New Zealand for the treatment of recurrent herpes labialis (cold sores) indication, therefore we do not have NZ specific usage data.

    Australian usage: FAMVIR® was first introduced in the UK in 1993 and has been marketed in Australia since 1996. It is used in long term suppression regimens as well as episodic treatment in courses of up to 7 days duration.

    Since launch in Australia, 29,000 units of the cold sores pack only have been sold. It is estimated that this is approximately 3-4 % of the total Pharmacy market on a year on year basis. The total annual antiviral market in Australia is estimated to be around $11 million with approximately 75 % sold through pharmacy and 25% through grocery. Approximately 1.3 million units of FAMVIR cold sore products ® were sold in the year ended February 2008.

This includes approximately 217,3000 units of FAMVIR® (500mg x 3) for cold sores Cold Sores on prescription.[1]

Global usage: It is difficult to achieve an accurate estimation of patients treated due to the variability of treatment regimens for each indication. This ranges from 250 mg two to three times a day to 750mg three times a day for a variable treatment period. To achieve an estimation of the number of patients treated, it has been assumed that each patient received an average total dose of 5 grams. The sales volume of FAMVIR® during the review period is approximately 53,000 kg famciclovir. Based on the assumption of 5 grams of FAMVIR® per treatment, we estimate that approximately 10.6 million patients have been treated between 2004-2006, when the most recent PSUR was issued.

Since launch of famciclovir in 1993, to 2005 there is an estimate of 10 million person-years of treatment (for all indications). During this period, a total of 2499 adverse reaction reports were recorded on the Novartis database. Common report terms in decreasing order of frequency are nausea, headache, rash, dizziness, confusional state, fatigue, pruritus, pain, pyrexia, malaise, urticaria, hallucinations and paraesthesia which are included in the Data Sheet (Appendix A).

As at 1 January 2008, Novartis estimates global usage of more than 10.6 million persons for the previous 3 year review period.

11. Labelling for the proposed new presentation(s)

Labelling of the current and proposed presentation is provided in Appendices D and E.

12. Proposed warning statements

- Label – "Keep out of reach of children"
- Data sheet: Current warnings remain.(see Appendix A)

13. Other products affected

None

[1] C-in-C, FAMVIR market research information

PART B - REASONS FOR REQUESTING CLASSIFICATION CHANGE

1. Benefits to the consumer and to the public expected from the proposed change

Benefits

The key benefit for consumers is the availability of a single day antiviral treatment of 3 x 500 mg tablets to effectively treat cold sores. Famvir® for cold sores is a convenient, one day treatment compared to the topical creams which need to be applied multiple times over a number of days (e.g. 5 times daily for 5 days, or every 2 hours). The single episode treatment pack delivers a precise dosing regimen and eliminates the variability that can be seen in the application of a quantity of topical cream.

This single dose aids compliance which can help minimise transmission of the virus and treats all secondary cold sores before eruption. As a Restricted Medicine, the pharmacist is well placed to counsel the patient on dosage, potential side effects, prevention of viral transmission, and the importance of treating the cold sore at the first sign of symptoms for any future outbreaks

Public Health

The use of famciclovir single dose at first sign of the recurrent cold sore is very simple and provides for better compliance, patient convenience, and, with pharmacist involvement, a good opportunity to reinforce other measures to prevent secondary infection and minimise spreading of the virus in the community.

All other treatments currently available for the condition are available without prescription (topical penciclovir –Pharmacy-Only; topical aciclovir or idoxuridine –General Sale; complementary medicines – unscheduled). Many of these are topical preparations which require multiple daily applications (e.g. topical aciclovir requires application 5 times daily for 5 days; topical penciclovir cream must be applied every 2 hours during the day for 4 days). For a complete list of available treatments, please refer to Appendix B.

During viral replication, spontaneous mutations in either or both of the thymidine kinase (TK) or DNA polymerase genes may cause the development of famciclovir-resistant strains to HSV. Mutation in the viral gene encoding TK is the most common mechanism, and leads to either:

- full loss of TK activity (TK negative)
- decreased levels of TK activity (TK partial), or
- a shift in the ability of viral TK to phosphorylate famciclovir without an equivalent loss in ability to phosphorylate thymidine (TK altered).

Approximately 95 % of HSV isolates are thymidine kinase deficient while the remaining are usually thymidine kinase altered, i.e. these mutants lack the expression or function of thymidine kinase. DNA polymerase mutants and TK/polymerase double mutants also exist; the latter is usually resistant to most antiviral compounds. The majority of commonly-encountered aciclovir-resistant TK negative mutants are also resistant to penciclovir [Morfin 2003].

Drug-resistant HSV from immunocompetent patients has remained at a rate of 0.1 - 0.7 % of isolates [Levin, Bacon, and Leary 2004]. Drug-resistant HSV is more commonly isolated from

immunocompromised patients and occurs at a rate of 4 - 7 % of isolates although the prevalence among these patients has also remained stable.

The results from penciclovir and famciclovir patient studies, including studies of up to four months' treatment with famciclovir, showed that no resistance occurred as a result of treatment with either famciclovir or penciclovir. Penciclovir-resistant isolates were found at the start of treatment or in the placebo groups in 0.25 % of the 1,976 total isolates from HSV and VZV (5/1976), and in 0.19 % of the 533 virus isolates from immunocompromised patients (1/533) (FAMVIR® approved Data Sheet – Appendix A).

In a susceptibility program using chronic suppressive treatment with penciclovir or famciclovir in immunocompetent and immunocompromised patients in 11 global clinical trials, there was no evidence of reduced penciclovir sensitivity in viral isolates obtained during or after treatment [Sarisky 2003].

In the immunocompetent population, the frequency of penciclovir-resistant HSV and aciclovir-resistant HSV are similar [Sarisky 2003]. The prevalence of HSV-resistant isolates from immunocompetent patients has remained more or less stable over many years of antiviral use, inclusive of long-term suppressive therapy for other indications. Also, resistance is 9-30-fold higher for HSV-2 than HSV-1 [Sarisky 2000].

The potential for promotion of resistance was discussed at the Australian TGA's DSEB Peer Review Meeting for FAMVIR® extension of indications on 22 December 2006 and the findings minuted as follows:

"In relation to the evaluator concerns about potential for promotion of resistance, the meeting considered that Herpes viruses have low rates (sic) of mutation and that there was substantial clinical experience that shows there is little treatment emergent resistance to penciclovir in herpes simplex viruses despite prolonged periods of patient treatment." [DSEB, 2006].

Sensitivity monitoring of HSV isolates during an extensive clinical program and a 5-year post-marketing period with valaciclovir confirmed a low rate of aciclovir resistance in immunocompetent patients (< 0.5 %) and immunocompromised patients (approximately 5 %) [Tyring 2002]. The isolates of immunocompetent patients who were treated with topical penciclovir for 4 days during successive episodes of recurrent *Herpes labialis* showed no significant change in sensitivity to penciclovir during or between treatments [Shin 2003].

No resistant isolates were found during the study although the proportion of resistant virus in successive clinical specimens tended to increase during each episode but returned to low levels at the start of each subsequent episode. This suggests a low risk of resistance in the immunocompetent host. The resistant virus accounts for a very small proportion of the total HSV population and there was no evidence of anti-viral resistant variants accumulating in the sensory ganglia of immunocompetent patients. Nucleoside analogue-resistant HSV-2 in immunocompetent patients is rare, even in those who received continuous antiviral prophylaxis for years. [Kreisel et al (2005)] reported only the third case of recurrent disease caused by a resistant virus.

HSV resistance to antiviral nucleoside analogues is rare. The extensive use of nucleoside analogues for the antiviral treatment of herpes infections for over 20 years has not been associated with an increased emergence of drug-resistance virus in immunocompetent or immunocompromised patients [Bacon 2003]. Given that this submission proposes a high and discrete dose, single day therapy and not a chronic suppressive therapy, viral resistance should not be an issue.

Patients are unlikely to gain access to famciclovir for recurrent outbreaks of cold sores if it remains as a Prescription Medicine. This is because they currently self-medicate with other OTC products such as topical aciclovir and have little reason to see a doctor. Also, as treatment is most effective when commenced during the prodromal period, effective medication needs to be at hand or easily accessible.

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

This proposal seeks to reschedule famciclovir for the treatment of a single episode of cold sores in immunocompetent patients as a Restricted Medicine. This would provide consumers with the opportunity for early intervention.

In order to be effective in the treatment of cold sores, there is only a narrow time window in which to initiate famciclovir therapy: treatment must be commenced at the earliest sign or symptom (within first 48 hours), before any skin or mucosa are damaged.

Currently, patients must seek advice from a general practitioner as soon as the signs or symptoms of cold sores are noted. Given the shortfall in numbers of doctors in some remote areas, and the need for some patients to make a prior appointment, patients may suffer considerable delay to treatment. Thus prior medical consultation is often impractical, creating a barrier to access for episodic treatment of cold sores.

Famciclovir is an effective treatment option with a favourable safety profile, administered in a convenient single dose for a condition that clearly meets the criteria for self-medication.

Famciclovir is safe when used correctly, and has been well tolerated in human studies, the most frequently reported adverse events from clinical trials being headache, fatigue and nausea, which were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment.

3. Relevant comparative data for like compounds

Currently registered treatments for *Herpes labialis* include the topical preparations, aciclovir (General Sale), penciclovir (Pharmacy Only) and idoxuridine (General Sale), and a host of other unscheduled over the counter medicines and complementary remedies that are primarily intended to provide symptomatic relief of cold sores while the disease runs its normal course. To the best of our knowledge, none of the latter unscheduled formulations have been tested for efficacy and safety under rigorous clinical trial conditions, as is the case for famciclovir.

The major advantage of using oral famciclovir therapy over any topical therapies for the treatment of cold sores is that all lesion sites are treated (i.e. primary and secondary), whereas topical therapy only treats the primary lesion sites to which the cream or solution is applied.

4. Local data or special considerations relating to NZ

As this product has not been marketed in New Zealand for the herpes labialis indication there is no local data available. We have however enclosed data on all cold sore preparations currently available in New Zealand (see Appendix B)

5. Interactions with other medicines

Clinical trial and post-marketing experience with famciclovir has not identified any drug interactions.

When famciclovir was administered 30 minutes after food, C_{max} was reduced and t_{max} was delayed, but systemic availability (AUC) was unaffected. Famciclovir should be taken at the first sign of symptoms, and without regard to meals.

The pharmacist is well placed to counsel patients on taking the product with or without food and the lack of any potential drug interactions with famciclovir.

6. Contraindications

There are no known contraindications apart from hypersensitivity to famciclovir (or penciclovir) and no clinically significant interactions have been identified.

7. Possible resistance

Viral resistance

HSV resistance to antiviral nucleoside analogues is rare. The extensive use of antiviral products for the treatment of herpes infections for over 20 years has not been associated with an increased emergence of drug-resistance virus in immunocompetent or immunocompromised patients [Bacon 2003]. In a susceptibility program involving 11 global clinical trials using chronic suppressive treatment with penciclovir or famciclovir in immunocompetent and immunocompromised patients, there was no evidence of reduced penciclovir sensitivity in viral isolates during or after treatment [Sarisky 2003]. Given the use in cold sores is a single day treatment regimen and not a chronic suppressive therapy, and that penciclovir is selectively activated in HSV infected cells only, viral resistance should not be an issue in this case.

8. Adverse events - nature, frequency etc.

The human toxicity profile of famciclovir is well characterised and the approved product information (Data Sheet) for famciclovir includes warnings and precautions based on safety information collected to date. Famciclovir has been well tolerated in human clinical studies. Headache, fatigue and nausea have been reported in clinical trials. These were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment.

Low incidence of severe adverse effects or side effects which are likely to require medical intervention

Famciclovir is well tolerated in human clinical studies and very few severe adverse effects have been reported in the post-marketing setting. In cold sore clinical trials, headache, fatigue and nausea have been reported most frequently and are generally mild or moderate in severity. Importantly, the incidences of these adverse events were comparable in patients receiving placebo treatment. Confusion, predominantly in the elderly, has also been reported rarely. Reports of serious side effects including skin reactions and thrombocytopenia are very rare in the post-marketing setting and close medical monitoring should not be required at the doses recommended for treating cold sore.

As the Famvir has not been marketed in New Zealand for cold sores there is currently no comparative data available from CARM, therefore we have enclosed as Appendix C ADRAC reports for cold sore preparations in Australia.

Famciclovir has been administered in courses lasting from one day to chronic administration for suppression of recurrent disease. Side effects are expected to be minimal during episodic treatment of cold sores in a single-day dosing regimen. The OTC presentation will clearly advise that dizziness, somnolence or confusion may arise and to avoid driving or operating machinery.

No clinically significant interactions have been identified with famciclovir or penciclovir. Evidence from preclinical studies has shown no potential for induction of cytochrome P_{450}. There have been only limited reports of acute overdosage, all of which have been asymptomatic.

These characteristics and the considerable post-marketing experience over a wide range of doses (including chronic administration) make a 1500 mg dose of famciclovir a suitable candidate for an OTC medicine.

As the pack represents a single treatment, there are no adverse effects expected if the entire pack is taken as this is the required dose. Additionally, the small pack size further limits the potential for an accidental overdose.

Pharmacists have considerable experience counselling patients with cold sores on the most appropriate treatment option. As a Restricted Medicine, a single day treatment with famciclovir represents an effective treatment option with a favourable safety profile, which can be dispensed to patients with appropriate counselling from a pharmacist.

9. Potential for abuse or misuse

Low abuse potential

There have been no reported cases of famciclovir abuse in clinical practice. The potential for famciclovir abuse would be equally unlikely as a Restricted Medicine. The product Famvir® for cold sores will be presented in a pack containing 3 x 500 mg tablets, which is sufficient for the treatment of a single episode of cold sores, further limiting any potential for intentional abuse.

Low potential for harm from inappropriate use

There is considerable clinical and post-marketing experience in immunocompetent and immunocompromised patients with high doses of famciclovir as well as chronic therapy with famciclovir. Famciclovir has a well established and favourable risk benefit profile so there is little potential for harm if used incorrectly by immunocompetent patients without cold sores or outside the prodromal period.

The use of famciclovir to treat cold sores is limited to patients over 18 years of age primarily due to nominal restrictions in the patient inclusion criteria in the pivotal trial. Whilst we have no intention to apply to reduce this age limit, it should be noted that the current Prescription product in Australia is also approved for use in children as young as 12 years old in other indications. There have been no cases of serious adverse effects reported in children. Therefore there would be a low potential for harm in either children or adolescents with a 3 x 500 mg tablet pack of famciclovir as a Restricted Medicine.

Also, the proposal to reschedule this pack to a Restricted Medicine should not increase the risk that children younger than 12 years might inadvertently take the product whilst at home. The product maintains the same risk as associated with any similar presentation of a prescription medicine and will be mitigated by the label warning to keep the product out of the reach of children.

Famciclovir is indicated for treatment of cold sores in **immunocompetent** adults. Adult **immunocompromised** patients with recurrent HSV infections including orofacial lesions require a different famciclovir dose taken over a number of days (500 mg bid for 7 days for episodic therapy; 500 mg bid for suppressive therapy). If immunocompromised patients gain access to OTC famciclovir, the 3 x 500 mg dosage is not likely to result in harm.

The product in its OTC presentation will be labelled only for treatment of cold sores and clearly indicate that its use is for cold sores (i.e. Famvir® for cold sores) and the pack size of 3 x 500mg tablets for a single treatment will limit the potential for any off-label use (see Appendices D and E for current Prescription Medicine and proposed Restricted Medicine labels). Some consumers may be aware of other uses/indications and there is the potential risk they may use it for recurrent genital herpes (RGH). This risk is considered minimal given intervention by the pharmacist at the point of sale and the price differential of an OTC cold sores 3 tablet pack versus the quantities available on prescription. In addition, the pack size and presentation of the product does not facilitate the correct dosing regimen required for RGH, providing further disincentive to intentional inappropriate use.

Please refer to Appendix C for a current list of adverse drug reactions for all cold sore preparations in Australia.

Safety in use with counselling by a pharmacist.

Pharmacists are well-placed to counsel on the safe use of famciclovir for the treatment of recurrent cold sores for the following reasons:

- Pharmacists have experience in counselling patients on other oral anti-infective agents, which are currently available as Pharmacist-Only medicines (for examples, see Table 2)
- Pharmacist have considerable experience in identifying and counselling patients on how to treat their cold sores

Table 2: Oral anti-infective agents which are currently available as a Restricted Medicines

Trade names	Active	Adult dosage regimen
Diflucan® One and generics	fluconazole	150 mg capsule as a single oral dose for vaginal candidiasis
Daktarin® Oral Gel (20 mg/mL)	miconazole	1.25 to 2.5 mL gel qid taken orally for at least a week after the symptoms have disappeared

The risk of masking a serious disease or compromising medical management of a disease can be managed by a pharmacist

Famciclovir treatment is unlikely to mask or compromise other medical conditions. Due to its prevalence in the community, generally most patients and pharmacists are readily able to recognise a recurrent cold sore..

It is conceivable that adult patients with recurrent HSV infections (including orofacial lesions) who are not overtly immunocompromised may be inadvertently dispensed the dose/pack of famciclovir which is intended for immunocompetent patients. It is expected Pharmacists will be able to identify patients who might not be overtly immunocompromised and direct them to their physician. Adult patients who are immunocompromised with recurrent HSV infections require a different famciclovir dose taken over a number of days (500 mg bid for 7 days for episodic therapy; 500 mg bid for suppressive therapy).

10. Abbreviations

AUC	Area under area under the serum concentration versus time curve
bid	2 times a day
C_{max}	Maximum peak serum concentration
DSEB	Drug Safety Evaluation Branch [of the TGA]
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
NDPSC	National Drugs and Poisons Schedule Committee
OTC	Over-the-counter (medicine)
PI	Product information
qid	4 times a day
RGH	Recurrent genital herpes
TGA	Therapeutic Goods Administration (a unit of the Australian Government Department of Health and Ageing)
t_{max}	Time at which the peak serum concentration maximum occurs (after initial drug administration)
VZV	Varicella zoster virus

PART C – SUPPORTING DATA

SUPPORTING DATA SUMMARY

APPENDIX A Current Prescription FAMVIR® Data Sheet and CMI

APPENDIX B Cold sore preparations from MIMs / IMS data – NZ
Cold sore preparations from ARTG - Australia

APPENDIX C ADRAC reports for cold sore products in Australia

APPENDIX D Current Prescription FAMVIR® 3 x 500 mg tablet pack carton

APPENDIX E Proposed Restricted Medicine FAMVIR ® for cold sores 3 x 500 mg tablet pack cartons (draft FAMVIR® for cold sores and FAMVIR Once® cartons)

BIBLIOGRAPHY

APPENDIX A: FAMVIR DATA SHEET.

This appendix contains the currently approved Data Sheet for FAMVIR®. The Data Sheet was approved by Medsafe on 23 November 2007.

DATA SHEET

FAMVIR®
Famciclovir
500 mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is famciclovir.

500 MG TABLETS

Each tablet contains 500 mg famciclovir.
This product is not able to deliver all approved dose regimens
For a full list of excipients, see List of excipients.

PHARMACEUTICAL FORM

Film-coated tablets

500 MG TABLETS

White, oval, biconvex tablets with or without (country specific) bevelled edges, debossed with "FAMVIR" or "FAMVIR 500" or "ORAVIR 500" or "FV 500" on one side and 500 or plain on the reverse side.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

Famvir® is indicated for the treatment of acute herpes zoster**,** including ophthalmic zoster and decreases the duration of associated post-herpetic neuralgia (PHN).
Famvir is indicated for the acute treatment of first episode and recurrences of genital herpes infections, and for the suppression of recurrent genital herpes.
Famvir is indicated for the treatment of recurrent herpes labialis (cold sores).
Famvir is also indicated in immunocompromised patients with herpes zoster or herpes simplex infections.

DOSAGE AND METHOD OF ADMINISTRATION

This product is not able to deliver all approved dose regimens

HERPES ZOSTER INFECTIONS IN IMMUNOCOMPETENT ADULTS

250 mg three times a day or 500 mg twice a day or 750 mg once a day for seven days for the treatment of the acute phase of herpes zoster. 500 mg three times a day for seven days for the

treatment of ophthalmic zoster. Treatment yields better results if initiated as soon as possible after rash onset. For those at risk of PHN, 250-500 mg three times a day for seven days, taken during the acute phase of the disease, to decrease the duration and incidence of PHN.

HERPES ZOSTER INFECTIONS IN IMMUNOCOMPROMISED ADULTS

500 mg three times daily for ten days. Initiation of treatment is recommended as soon as possible after rash onset.

HERPES SIMPLEX INFECTIONS IN IMMUNOCOMPETENT ADULTS

- First episode of genital herpes

  250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after onset of lesions.

- Recurrent genital herpes

  1000 mg twice daily for one day or 125 mg twice daily for five days. Initiation of treatment is recommended during the prodromal period or as soon as possible after onset of lesions.

- Recurrent herpes labialis (cold sores)

  1500 mg as a single dose for one day. Initiation of treatment is recommended at the earliest sign or symptom of a cold sore (e.g. tingling, itching or burning).

HERPES SIMPLEX INFECTIONS IN IMMUNOCOMPROMISED ADULTS

500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after rash onset.

SUPPRESSION OF RECURRENT GENITAL HERPES INFECTIONS

250 mg twice daily. The length of treatment depends on the severity of the disease. Therapy should be re-evaluated after 12 months in order to observe possible changes in the natural history of the disease. A dose of 500 mg b.i.d has been shown to be efficacious in HIV patients.

DOSAGE IN RENALLY IMPAIRED PATIENTS

Because reduced clearance of penciclovir, the antivirally active metabolite of famciclovir (see Pharmacokinetic properties), is related to reduced renal function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function. The following modifications in dosage are recommended:

HERPES ZOSTER INFECTIONS IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥ 40	250 mg/500 mg t.i.d. or 500 mg b.i.d. for 7 or 10 days*
30-39	250 mg t.i.d. or 250 mg b.i.d. for 7 or 10 days*
10-29	125 mg t.i.d. or 125 mg b.i.d. for 7 or 10 days*

** 7 days in immunocompetent patients, 10 days in immunocompromised patients.*

HERPES SIMPLEX INFECTIONS IN IMMUNOCOMPETENT PATIENTS

- **First episode genital herpes**

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥ 30	250 mg t.i.d. for 5 days
10-29	125 mg t.i.d. for 5 days

- **Recurrent genital herpes**

1. Adjustments for single-day regimen

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥60	1000 mg b.i.d for 1 day
40-59	500 mg b.i.d for 1 day
20-39	500 mg single dose
<20	250 mg single dose

2. Adjustments for 5-day regimen

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥ 10	125 mg b.i.d for 5 days

- **Recurrent herpes labialis (cold sores)**

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥60	1500 mg single dose
40-59	750 mg single dose
20-39	500 mg single dose
<20	250 mg single dose

HERPES SIMPLEX INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥ 40	500 mg b.i.d for 7 days
30-39	250 mg b.i.d for 7 days
10-29	125 mg b.i.d for 7 days

SUPPRESSION OF RECURRENT GENITAL HERPES INFECTIONS

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥ 30	250 mg b.i.d
10-29	125 mg b.i.d

RENALLY IMPAIRED PATIENTS ON HAEMODIALYSIS

Since 4 h haemodialysis results in approximately 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis.
For patients with herpes zoster, the recommended dose is 250 mg after each dialysis.
For patients with recurrent genital herpes, famciclovir should be administered either in a single dose of 250 mg following dialysis (single-day regimen), or 125 mg following each dialysis (multiple-day regimen).
For patients with recurrent herpes labialis (cold sores), famciclovir should be administered in a single dose of 250 mg following dialysis (single-day regimen).

HEPATICALLY IMPAIRED PATIENTS

No dosage adjustment is required in patients with well-compensated hepatic impairment. No data are available for patients with severe uncompensated hepatic impairment (see Pharmacokinetic properties).

ELDERLY

Dosage modification is not required unless renal function is impaired.

DOSAGE IN CHILDREN

The efficacy and safety of famciclovir has not been investigated in children. Famciclovir should therefore not be used in children unless the potential benefits are considered to justify the potential risks associated with treatment.

MAXIMUM TOLERATED DAILY DOSE AND DURATION

Herpes zoster patients receiving 750 mg three times daily for seven days tolerated the Famvir therapy well. Genital herpes patients receiving up to 750 mg three times daily for 5 days, and up to 500 mg three times daily for 10 days also tolerated the product well. Good tolerance was also seen in two 12 month studies, in which genital herpes patients received doses of up to 250 mg three times daily. Similar tolerance was experienced in immunocompromised herpes zoster patients receiving up to 500 mg three times daily for 10 days and herpes simplex patients receiving up to 500 mg twice daily for 7 days and 500 mg twice daily for 8 weeks.

MODE OF ADMINISTRATION

Because the systemic availability (AUC) of penciclovir was not altered when famciclovir was administered with food, it appears that famciclovir can be taken without regard to meals (see Pharmacokinetic properties).
For some patients i.v penciclovir may be more appropriate than famciclovir, the oral prodrug of penciclovir. While the decision on the best patient management and mode of administration should rest with the physician, in severely ill patients initiation of therapy with i.v penciclovir should be considered.

CONTRAINDICATIONS

Famvir is contraindicated in patients with known hypersensitivity to famciclovir or other constituents of Famvir. It is also contraindicated in those patients who have shown hypersensitivity to penciclovir.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special attention should be paid to patients with impaired renal function and dosage adjustment is necessary (see Dosage and method of administration and Overdose). No special precautions are required for elderly patients with normal renal function and patients with well-compensated hepatic impairment. Famciclovir has not been studied in patients with severe uncompensated hepatic impairment (see Pharmacokinetic properties).
Genital herpes is a sexually transmitted disease. The risk of transmission is increased during acute episodes. Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated.
During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still theoretically possible. Patients should therefore take appropriate steps for protected intercourse.
Famvir 125 mg, 250 mg and 500 mg tablets contain lactose (26.9 mg, 53.7 mg and 107.4 mg, respectively). Patients with rare hereditary problems of galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption should not take Famvir 125 mg, 250 mg and 500 mg

tablets.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

EFFECTS OF OTHER MEDICINAL PRODUCTS ON FAMCICLOVIR

Probenecid and other drugs that affect renal physiology could affect plasma levels of penciclovir (active metabolite of famciclovir, see Pharmacokinetic properties).
No clinically significant alterations in penciclovir pharmacokinetics were observed following single-dose administration of 500 mg famciclovir after pre-treatment with multiple doses of allopurinol, cimetidine, theophylline, zidovudine, or promethazine or when given shortly after an antacid (magnesium and aluminium hydroxide), or concomitantly with emtricitabine. No clinically significant effect on penciclovir pharmacokinetics was observed following multiple-dose (t.i.d.) administration of famciclovir (500 mg) with multiple doses of digoxin.
The conversion of the inactive metabolite 6-deoxy penciclovir (formed by deacetylation of famciclovir) to penciclovir is catalysed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme and/or inhibiting this enzyme could potentially occur. Clinical interaction studies of famciclovir with cimetidine and promethazine, *in vitro* inhibitors of aldehyde oxidase, did not show relevant effects on the formation of penciclovir. However. raloxifene, the most potent aldehyde oxidase inhibitor observed *in vitro*, could affect the formation of penciclovir.

EFFECTS OF FAMCICLOVIR ON OTHER MEDICINAL PRODUCTS

The pharmacokinetics of digoxin were not altered by concomitant administration of single or multiple (t.i.d) doses of famciclovir (500 mg). No clinically significant effects on the pharmacokinetics of zidovudine, its metabolite zidovudine glucuronide or emtricitabine were observed following a single oral dose of 500 mg famciclovir co-administered with zidovudine or emtricitabine.
Although famciclovir is only a weak inhibitor of aldehyde oxidase *in vitro,* interactions with drugs metabolized by aldehyde oxidase could potentially occur.Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

PREGNANCY AND LACTATION

PREGNANCY

Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir, the safety of famciclovir in human pregnancy has not been established. Famciclovir should therefore not be used during pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

LACTATION

Studies in rats show that penciclovir is excreted in the breast milk of lactating females given oral Famvir (famciclovir). There is no information on excretion in human milk. Famciclovir should not be used in nursing mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that Famvir will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous

system disturbances while taking Famvir should refrain from driving or operating machinery.

ADVERSE EFFECTS

Famciclovir has been well tolerated in human studies. Headache and nausea have been reported in clinical trials. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment.

The following table specifies the estimated frequency of adverse reactions based on all the spontaneous reports and literature cases that have been reported for Famvir since its introduction to the market.

Adverse reactions (Table 1) are ranked under headings of frequency, using the following convention: *very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (<1/10,000),* including isolated reports.

TABLE 1

Blood and lymphatic system disorders		
	Very rare:	Thrombocytopenia.
Psychiatric disorders		
	Rare:	Confusion (predominantly in the elderly).
	Very rare:	Hallucinations.
Nervous system disorders		
	Rare:	Headache.
	Very rare:	Dizziness, somnolence (predominantly in the elderly).
Gastrointestinal disorders		
	Rare:	Nausea.
	Very rare:	Vomiting.
Hepatobiliary disorders		
	Very rare:	Cholestatic jaundice, abnormal liver function tests.
Skin and subcutaneous tissue disorders		
	Very rare:	Rash, pruritus, urticaria, serious skin reactions (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis).

Famciclovir has also been well tolerated in immunocompromised patients. Adverse effects reported from clinical studies were similar to those reported in the immunocompetent population.

OVERDOSE

Overdose experience with famciclovir is limited. A report of accidental acute overdosage (10.5 g) was asymptomatic. In a report of chronic use (10 g/day for two years), famciclovir was well tolerated. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dosage has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 h haemodialysis.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Oral antiviral agent, ATC code: JO5A B09
Famciclovir is the oral form of penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has demonstrable *in vitro* activity against herpes simplex viruses (HSV types 1 and 2), varicella zoster virus, Epstein-Barr virus and cytomegalovirus.

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir. In virus-infected cells penciclovir is rapidly and efficiently converted into a triphosphate (mediated via virus-induced thymidine kinase). This triphosphate persists in infected cells in excess of 12 hours and inhibits replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Hence the probability of toxicity to mammalian host cells is low and uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

The most common form of resistance encountered with acyclovir among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would be expected to be cross-resistant to both penciclovir and acyclovir. However, penciclovir has been shown to be active against a recently isolated acyclovir-resistant herpes simplex virus strain with an altered DNA polymerase.

In a study in suppression of recurrent genital herpes in which immunocompetent patients were treated with famciclovir for 4 months, there was no evidence of resistance to famciclovir when isolates from 71 patients were analysed.

Results from penciclovir and famciclovir patient studies, including studies of up to four months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.3% in the 981 total isolates tested to date and 0.19% in the 529 virus isolates from immunocompromised patients. The resistant isolates were found at the start of treatment or in a placebo group, with no resistance occurring on or after treatment with famciclovir or penciclovir. A placebo controlled study has demonstrated that famciclovir significantly reduces the duration of post-herpetic neuralgia when administered to patients with herpes zoster.

A placebo controlled study in patients with immunodeficiency due to HIV has shown that famciclovir 500 mg b.i.d significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

In a large clinical trial, famciclovir was shown to be effective and well tolerated in the treatment of ophthalmic zoster.

PHARMACOKINETIC PROPERTIES

GENERAL CHARACTERISTICS

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir is 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/mL, 1.6 micrograms/mL, 3.3 micrograms/mL and 5.1 micrograms/mL respectively, and occurred at a median time of 45 minutes post-dose. The extent of

systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food. Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir, is approximately 2 hours. There is no accumulation of penciclovir on repeated dosing with famciclovir. Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins.

Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine and no unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.

CHARACTERISTICS IN SPECIAL POPULATIONS

PATIENTS WITH HERPES ZOSTER INFECTION

Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir. The terminal plasma half-life of penciclovir in patients with herpes zoster was 2.8 h and 2.7 h, respectively, after single and repeated doses of famciclovir.

SUBJECTS WITH RENAL INSUFFICIENCY

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal insufficiency (see Posology and method of administration).

SUBJECTS WITH HEPATIC INSUFFICIENCY

Well-compensated chronic liver disease had no effect on the extent of systemic availability of penciclovir following oral famciclovir. No dose adjustment is recommended for patients with well-compensated hepatic impairment (see Posology and method of administration and Special warnings and precautions for use). The pharmacokinetics of penciclovir have not been evaluated in patients with severe uncompensated hepatic impairment.

ELDERLY SUBJECTS

Based on cross-study comparisons, the mean penciclovir AUC was about 40 % higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see Dosage and method of administration).

GENDER

Small differences in renal clearance of penciclovir between females and males have been reported and were attributed to gender differences in renal function. No dose adjustment based on gender is recommended.

PRECLINICAL SAFETY DATA

CARCINOGENICITY

In 2 year studies there were no changes seen at 200 mg/kg/d. At the maximally tolerated dose of 600 mg/kg/d in female rats there was an increased incidence of mammary adenocarcinoma, a common tumour in this strain of rats used in the studies. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

GENOTOXICITY

Famciclovir was not found to be genotoxic in a comprehensive battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and repairable damage to DNA. Penciclovir, in common with other drugs of this class, has been shown to cause chromosomal damage, but did not induce gene mutation in bacterial or mammalian cell systems, nor was there evidence of increased DNA repair *in vitro*.

REPRODUCTIVE TOXICITY

Famciclovir is well tolerated in laboratory animals. In common with other drugs of this class, degenerative changes of the testicular epithelium were noted.
Famciclovir has been shown to have no significant effects on sperm count, morphology, or motility in man. Impaired fertility was observed in male rats given 500 mg/kg. There were no significant effects on fertility in female rats given famciclovir.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

500 MG TABLETS

Tablet core: hydroxypropyl cellulose, lactose anhydrous (country specific), sodium starch glycollate, magnesium stearate.
Tablet coating: hypromellose, polyethylene glycol 4000, polyethylene glycol 6000, titanium dioxide (E 171).

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

3 years.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C. Store in the original package.
Famvir must be kept out of the reach and sight of children.

NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/aluminium blister packs.

500 mg: blister packs contain 3 tablets.

SPECIAL PRECAUTIONS FOR DISPOSAL

No specific instructions.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS

Novartis New Zealand limited
Private Bag 47909
Ponsonby
6-8 Macklevie Street
Grey Lynn
AUCKLAND
Telephone: 09 361 8100

DATE OF PREPARATION

7 September 2007
(Ref: BPI 29 August 2007)

APPENDIX B

Cold Sore products available in the New Zealand Market – the following lists have been prepared from MIMs and IMS data

TRADE NAME	DOSAGE FORM	INGREDIENTS	QUANTITY	UNITS	PACK SIZE	CLASSIFICATION	INDICATION
Betadine Cold Sore	**Paint**	Povidone iodine; ethanol	10	%	8 ml	General Sale	Cold sores
	Pain Relief	Povidone iodine, lauromacrogol 400 mg/ml; ethanol	10	%	8 ml	General Sale	Cold sores
	Ointment	Povidone iodine; polyethylene glycol base	10	%	7.5 g	General Sale	Cold sores
Egoderm	**Ointment**	Ichthammol 1%, zinc oxide 15%; hydroxybenzoates, dimethicone 1.6%; petrolatum base, lanolin free			25 g	General Sale	Subacute dermatitis and eczema; tender, itchy or broken skin rashes; anogenital inflammation; nappy rash; minor cold sores; following or as an alternative to corticosteroids in subacute skin conditions. Contraindications: Acute weeping dermatoses
	Ointment	Ichthammol 1%, zinc oxide 15%; hydroxybenzoates, dimethicone 1.6%; petrolatum base, lanolin free			50 g	General Sale	Subacute dermatitis and eczema; tender, itchy or broken skin rashes; anogenital inflammation; nappy rash; minor cold sores; following or as an alternative to corticosteroids in subacute skin conditions. Contraindications: Acute weeping dermatoses
Vectavir	**Cream**	Penciclovir	1	%w/w	2g 5g	Pharmacy Only	Antiviral. Recurrent cold sores (herpes labialis) in adults and children ≥ 12 years.

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Viraban	**Ointment**	Aciclovir; polyethylene glycol.	5	%	5 g	General Sale	Purine analogue, antiviral. Treatment of HSV infection of lips and face.
Virasolve	**Cream**	Idoxuridine 5mg, lignocaine hydrochloride 20mg and benzalkonium chloride 5mg			5g	General Sale	Virasolve is formulated to act against cold sores in three ways - it contains an antiviral (idoxuridine) to fight the cold sore virus, it contains an antibacterial (benzalkonium chloride) to prevent infection and an anaesthetic (lignocaine hydrochloride) to relieve pain and itching.
Viratac	**Cream**	Aciclovir BP.	5	%	5 g	General Sale	Purine analogue, antiviral. Treatment of cold sores
Zovirax	**Cold Sore Cream**	Aciclovir; propylene glycol; water miscible base.	5	%	2 g (tube) 2 g (pump pack)	General Sale	Purine analogue, antiviral. Treatment of HSV infection of the lips and face (herpes labialis).

New Zealand, Total Market, Combined NPI/NHI, Total Form, Total ATC, Total Molecule

	Values			Values Growth (Prv Yr)		
	MAT Sep 2006	MAT Sep 2007	MAT Sep 2008	MAT Sep 2006	MAT Sep 2007	MAT Sep 2008
ZOVIRAX CSC	2,686,195	2,638,615	2,347,254	10.14	-1.77	-11.04
ALDARA	809,894	761,318	856,593	8.82	-6.0	12.51
LOVIR	5,722	469,104	668,108	-39.95	8,098.25	42.42
CONDYLINE	202,080	229,204	223,498	1.49	13.42	-2.49
VIRASOLVE	168,582	177,405	185,239	-15.51	5.23	4.42
VIRATAC COLD SORE	180,042	148,602	156,562	-12.81	-17.46	5.36
VECTAVIR	110,714	112,676	92,164	333.29	1.77	-18.2
AFT VIRABAN	41,617	22,666	76,584	-39.57	-45.54	237.88
WARTEC	1,550	682	496	13.64	-56.0	-27.27

New Zealand, Total Market, Combined NPI/NHI, Total Form, Total ATC, Total Molecule

	Units			Units Growth (Prv Yr)		
	MAT Sep 2006	MAT Sep 2007	MAT Sep 2008	MAT Sep 2006	MAT Sep 2007	MAT Sep 2008
ZOVIRAX CSC	197,500	193,854	172,443	6.06	-1.85	-11.04
LOVIR	622	87,279	119,979	-39.96	13,931.99	37.47
VIRASOLVE	27,591	29,035	30,317	-15.5	5.23	4.42
VIRATAC COLD SORE	19,133	15,766	16,585	-12.81	-17.6	5.19
VECTAVIR	11,127	11,324	9,633	333.29	1.77	-14.93
AFT VIRABAN	5,564	2,420	8,147	-39.57	-56.51	236.65
ALDARA	6,785	6,896	7,759	25.81	1.64	12.51
CONDYLINE	6,315	6,293	6,375	1.49	-0.35	1.3
WARTEC	25	11	8	13.64	-56.0	-27.27

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	Values					
	MAT Jun 2007	MAT Jun 2008	Growth	YTD07	YTD08	Growth
Total Product	4,071,682	4,028,457	-1.1%	1,987,504	2,049,213	3.1%
AFT VIRABAN	1,263	82,344	6419.7%	44	30,279	68715.9%
CONDYLINE	221,254	226,474	2.4%	119,206	110,422	-7.4%
WARTEC	806	372	-53.8%	310	248	-20.0%
LOVIR	497		-100.0%			#DIV/0!
ZOVIRAX CSC	2,621,549	2,480,880	-5.4%	1,277,230	1,263,795	-1.1%
ALDARA	781,741	786,490	0.6%	374,697	411,019	9.7%
VIRASOLVE	174,283	194,484	11.6%	89,709	102,888	14.7%
VIRATAC COLD SORE	157,016	155,590	-0.9%	74,019	75,096	1.5%
VECTAVIR	113,273	101,823	-10.1%	52,289	55,466	6.1%
Coldsore Sales		**3,015,121**			**1,527,524**	

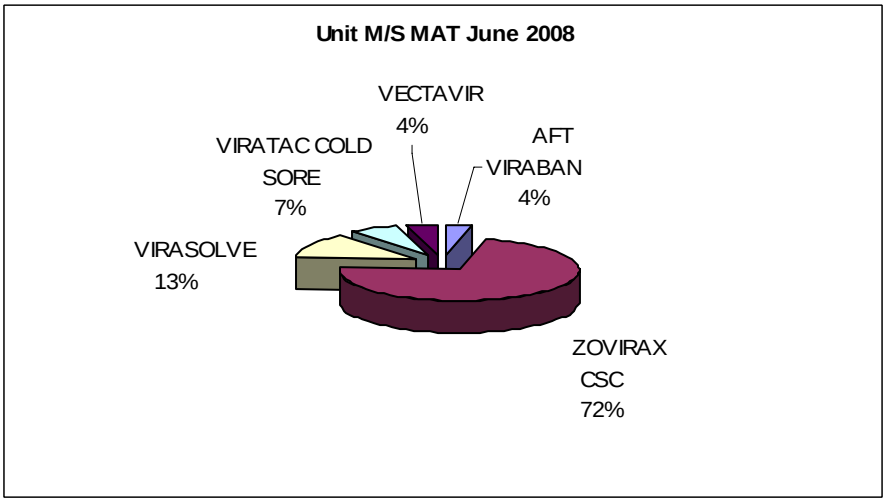
	Segment Share - Values					
	MAT Jun 2007	MAT Jun 2008	Growth pts	YTD07	YTD08	Growth pts
AFT VIRABAN	0.0%	2.0%	2.0%	0.0%	1.5%	1.5%
CONDYLINE	5.4%	5.6%	0.2%	6.0%	5.4%	-0.6%
WARTEC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
LOVIR	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
ZOVIRAX CSC	64.4%	61.6%	-2.8%	64.3%	61.7%	-2.6%
ALDARA	19.2%	19.5%	0.3%	18.9%	20.1%	1.2%
VIRASOLVE	4.3%	4.8%	0.5%	4.5%	5.0%	0.5%
VIRATAC COLD SORE	3.9%	3.9%	0.0%	3.7%	3.7%	-0.1%
VECTAVIR	2.8%	2.5%	-0.3%	2.6%	2.7%	0.1%

	MAT		
AFT VIRABAN	82,344	**AFT VIRABAN**	30,279
ZOVIRAX CSC	2,480,880	**ZOVIRAX CSC**	1,263,795
VIRASOLVE	194,484	**VIRASOLVE**	102,888
VIRATAC COLD SORE	155,590	**VIRATAC COLD SORE**	75,096
VECTAVIR	101,823	**VECTAVIR**	55,466

Units					
MAT Jun 2007	MAT Jun 2008	Growth	YTD07	YTD08	Growth
262,824	263,161	0.1%	128,169	133,555	4.2%
169	8,760	5083.4%	6	3,221	53583.3%
6,326	6,267	-0.9%	3,137	3,213	2.4%
13	6	-53.8%	5	4	-20.0%
54		-100.0%			#DIV/0!
192,599	182,252	-5.4%	93,836	92,819	-1.1%
7,081	7,124	0.6%	3,394	3,723	9.7%
28,524	31,830	11.6%	14,682	16,839	14.7%
16,674	16,482	-1.2%	7,854	7,955	1.3%
11,384	10,440	-8.3%	5,255	5,781	10.0%
	249,764				

Segment Share - Units					
MAT Jun 2007	MAT Jun 2008	Growth pts	YTD07	YTD08	Growth pts
0.1%	3.3%	3.3%	0.0%	2.4%	2.4%
2.4%	2.4%	0.0%	2.4%	2.4%	0.0%
0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
73.3%	69.3%	-4.0%	73.2%	69.5%	-3.7%
2.7%	2.7%	0.0%	2.6%	2.8%	0.1%
10.9%	12.1%	1.2%	11.5%	12.6%	1.2%
6.3%	6.3%	-0.1%	6.1%	6.0%	-0.2%
4.3%	4.0%	-0.4%	4.1%	4.3%	0.2%

AFT VIRABAN	8,760
ZOVIRAX CSC	182,252
VIRASOLVE	31,830
VIRATAC COLD SORE	16,482
VECTAVIR	10,440



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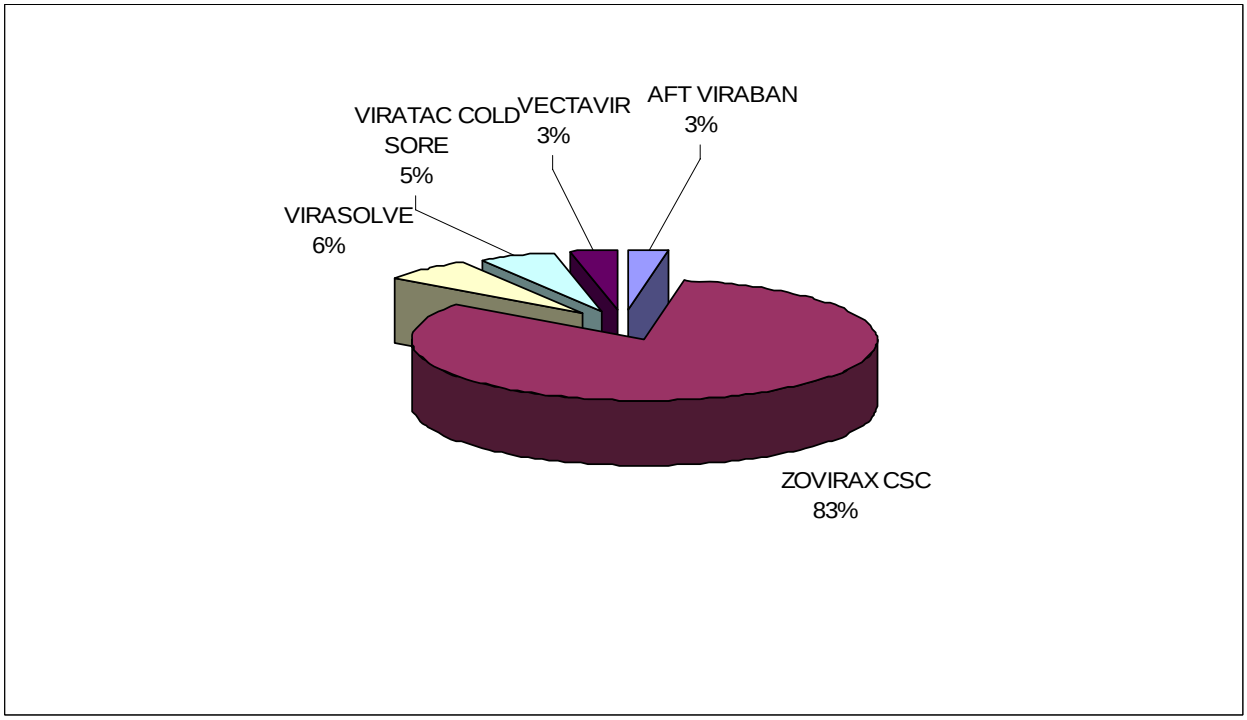
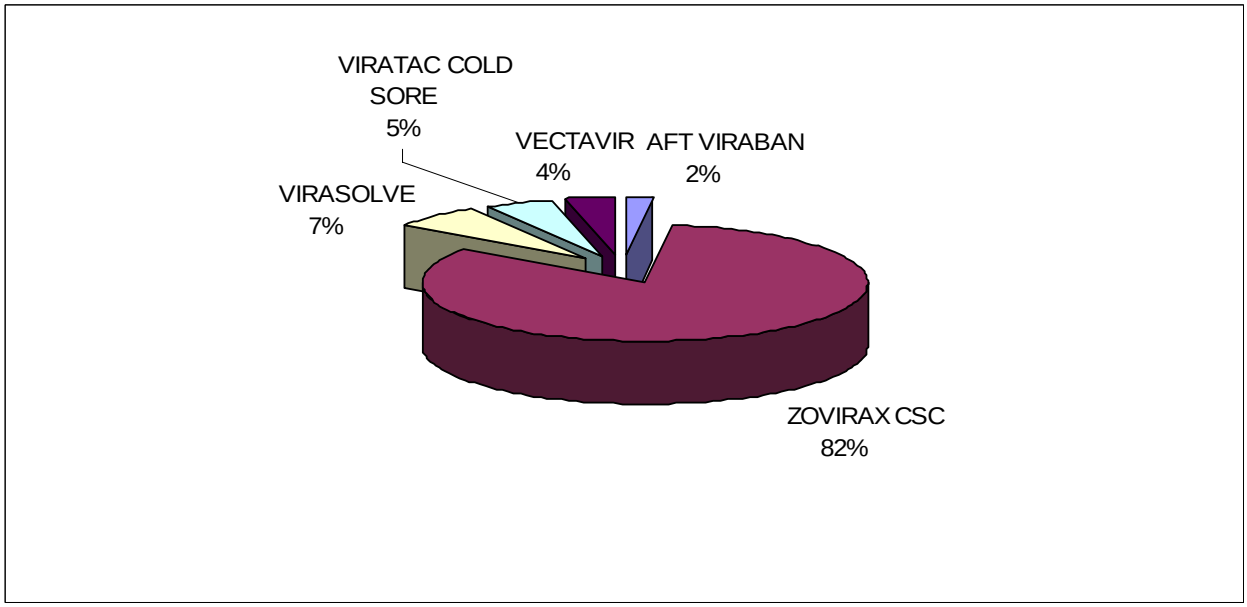

VIRATAC COLD SORE 5%
VECTAVIR 3%
AFT VIRABAN 3%
VIRASOLVE 6%
ZOVIRAX CSC 83%

YTD


VIRATAC COLD SORE 5%
VECTAVIR 4%
AFT VIRABAN 2%
VIRASOLVE 7%
ZOVIRAX CSC 82%

PATIENT FLOW

% of patients on Famvir		**10%**	**20%**	**30%**	**40%**
High Frequency (6-12x) patients	**50,560**	5056	10112	15168	20224
Price	**$17.79**	$89,946	$179,892	$269,839	$359,785
Number of scripts per patient	**2**	$179,892	$359,785	$539,677	$719,570
% of patients on Famvir		**5%**	**10%**	**15%**	**20%**
Frequent (3-4x) patients	**120,080**	6004	12008	18012	24016
	1	$106,811	$213,622	$320,433	$427,245
Number of scripts per patient	**2**	$213,622	$427,245	$640,867	$854,489
High frequency & Frequent	**Total**	**$393,515**	**$787,030**	**$1,180,544**	**$1,574,059**
% of patients on Famvir		**10%**	**20%**	**30%**	**40%**
Patients visting GP	**17,064**	1706	3413	5119	6826
	1	$30,357	$60,714	$91,071	$121,427
Number of scripts per patient	**2**	$60,714	$121,427	$182,141	$242,855

AUD	$ 16.57
NZD	$ 20.46
AUD	$ 17.79
NZD	$ 21.96

COMPARISONS

	Famvir	**aciclovir**	**Vectavir**	**Compeed**	**Virasolve**	**aciclovir gen**
Form	Tablet	Cream	Cream	Patch	Cream	Cream
Dose	1500mg	Topical	Topical	Topical	Topical	Topical
Frequency	Stat	5x Day	2 Hrly	8hrly	Hrly 1st day	5x Day
Duration	Single Dose	5 Days	4 days	5 Days	5 Days	5 Days
Lesion Healing (Days)*	2	0.5-0.6				0.5-0.6
Cost		$23.00	$14.95	$22.50	$13.50	$18.50
No of Treatments	1	>1	>1	>1	>1	>1
Author	Spruance	Spruance				

**Improvement vs. placebo*

APPENDIX C - ADRAC REPORTS FOR COLD SORE PREPARATIONS

ADRAC REPORTS FOR COLD SORE PREPARATIONS

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

BETADINE SORE THROAT GARGLE — Layer 1 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		9	6
- Occurrences of Medicine		9	6
- Reactions Related to Medicine		23	11
Congenital, familial and genetic disorders	Goitre congenital	1	1
Gastrointestinal disorders	Abdominal pain	1	0
General disorders and administration site conditions	Application site reaction	1	1
	Chills	1	0
	Pyrexia	1	0
	Face oedema	1	1
Hepatobiliary disorders	Jaundice	1	0
	Hepatitis	1	0
Nervous system disorders	Ataxia	1	0
Psychiatric disorders	Confusional state	1	0
Respiratory, thoracic and mediastinal disorders	Cough	1	1
	Dysphonia	1	1
Skin and subcutaneous tissue disorders	Dermatitis bullous	1	0
	Dry skin	1	1
	Rash erythematous	2	1
	Skin exfoliation	1	1
	Pruritus	3	2
	Dermatitis psoriasiform	1	0
	Rash	1	1
	Rash maculo-papular	1	0

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

BETADINE COLD SORE — Layer 2 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		1	1
- Occurrences of Medicine		1	1
- Reactions Related to Medicine		1	1
Skin and subcutaneous tissue disorders	Alopecia	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ACICLOVIR — Layer 3 of 17

		ALL REPORT DATES		
		Causality Unclear Excluded		
		Total	Death Outcome	Sole Suspected
- Cases Including Medicine		506	9	309
- Occurrences of Medicine		517	9	309
- Reactions Related to Medicine		957	15	587
Blood and lymphatic system disorders	Anaemia	1	0	0
	Hypochromic anaemia	1	0	1
	Pancytopenia	2	0	0
	Coombs positive haemolytic a	1	0	0
	Haemolysis	1	0	0
	Thrombocytopenia	7	0	2
	Red blood cell abnormality	1	0	1
	Eosinophilia	1	0	0
	Leukopenia	2	0	0
	Agranulocytosis	1	0	0
	Neutropenia	11	0	0
Cardiac disorders	Atrioventricular block	1	0	1
	Extrasystoles	2	0	0
	Tachycardia	3	0	2
	Atrial fibrillation	1	0	1
	Supraventricular tachycardia	1	0	0
	Cardiac arrest	1	1	1
	Cyanosis	1	0	0
	Palpitations	7	0	5
	Myocardial infarction	1	0	0
	Left ventricular failure	1	0	0
	Cardiomyopathy	1	0	0
Congenital, familial and genetic disorders	Multiple congenital abnormalit	2	0	0
	Cataract congenital	1	0	1
Ear and labyrinth disorders	Deafness	1	0	0
	Tinnitus	2	0	0
	Vertigo	3	0	3
Endocrine disorders	Inappropriate antidiuretic horr	1	0	1

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ACICLOVIR					Layer 3 of 17
Endocrine disorders	Hypothyroidism	1	0	0	
Eye disorders	Conjunctivitis	2	0	2	
	Keratitis	2	0	2	
	Ulcerative keratitis	1	0	1	
	Mydriasis	1	0	0	
	Photophobia	5	0	2	
	Accommodation disorder	1	0	1	
	Diplopia	1	0	0	
	Visual disturbance	6	0	4	
Gastrointestinal disorders	Pancreatitis acute	1	0	0	
	Rectal haemorrhage	2	0	2	
	Colitis	1	0	1	
	Oesophagitis	1	0	0	
	Diarrhoea	11	0	10	
	Dyspepsia	2	0	2	
	Abdominal pain	8	1	1	
	Dysphagia	2	0	1	
	Nausea	40	0	32	
	Vomiting	25	0	17	
	Steatorrhoea	1	0	0	
	Cheilitis	1	0	1	
	Lip blister	1	0	0	
	Aphthous stomatitis	1	0	1	
	Mouth ulceration	1	0	0	
	Stomatitis	2	0	2	
	Ascites	1	0	0	
	Dry mouth	2	0	2	
	Salivary hypersecretion	1	0	1	
	Salivary gland enlargement	1	0	0	
	Glossitis	3	0	3	
	Tongue oedema	2	0	1	
General disorders and administration site conditions	Application site oedema	1	0	1	
	Application site reaction	40	0	39	
	Infusion site vesicles	1	0	0	
	Injection site extravasation	1	0	1	

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ACICLOVIR					Layer 3 of 17
General disorders and administration site conditions	Injection site pain	1	0	1	
	Injection site reaction	13	0	13	
	Chills	2	0	1	
	Pyrexia	14	0	4	
	Death	1	1	1	
	Sudden death	1	1	0	
	Asthenia	2	0	2	
	Fatigue	6	0	3	
	Malaise	13	0	10	
	Gait disturbance	2	0	2	
	Thirst	1	0	1	
	Ulcer	1	0	1	
	Face oedema	19	0	16	
	Oedema	3	0	2	
	Oedema peripheral	5	0	4	
	Chest pain	4	0	3	
	Discomfort	1	0	1	
	Pain	6	0	6	
	Drug ineffective	20	0	19	
	Therapeutic response decrea	3	0	2	
	Therapeutic response unexpe	2	0	1	
Hepatobilliary disorders	Hepatitis cholestatic	2	0	0	
	Jaundice	4	0	2	
	Hepatic function abnormal	22	1	6	
	Hepatic failure	2	1	0	
	Hepatic steatosis	2	0	0	
	Hepatitis	4	0	2	
	Hepatocellular injury	1	0	1	
Immune system disorders	Hypersensitivity	3	0	2	
	Anaphylactoid reaction	1	0	0	
Infections and infestations	Candidiasis	1	0	0	
	Pneumonia	1	0	0	
	Sepsis	2	1	0	
	Rash pustular	1	0	1	
	Pharyngitis	4	0	3	

ACICLOVIR					Layer 3 of 17
Infections and infestations	Varicella	1	0	1	
Injury, poisoning and procedural complicatic	Medication error	1	0	1	
Investigations	Blood creatine phosphokinase	1	0	0	
	Red blood cell sedimentation	1	0	1	
	Liver function test abnormal	1	0	0	
	Weight decreased	2	0	1	
	Blood creatinine increased	7	0	5	
	Blood urea increased	1	0	1	
	Crystal urine	1	0	1	
	Drug level decreased	1	0	0	
Metabolism and nutrition disorders	Lactic acidosis	1	1	0	
	Acidosis	1	0	0	
	Anorexia	5	0	2	
	Hypokalaemia	1	0	0	
	Hyponatraemia	4	0	2	
	Dehydration	1	0	1	
	Diabetes mellitus	2	0	1	
	Hyperglycaemia	4	0	1	
	Hypoglycaemia	1	0	0	
	Hypercholesterolaemia	3	0	0	
	Hypertriglyceridaemia	4	0	0	
	Hyperlipidaemia	1	0	0	
Musculoskeletal and connective tissue disorders	Arthritis	2	0	2	
	Arthropathy	1	0	0	
	Arthralgia	5	0	5	
	Osteoarthritis	1	0	0	
	Myalgia	10	1	9	
	Muscle atrophy	2	1	0	
	Myopathy	1	0	0	
	Back pain	1	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	1	0	0	
	Angiolipoma	1	0	0	
Nervous system disorders	IIIrd nerve paralysis	1	0	0	
	Facial palsy	1	0	1	
	Encephalopathy	9	0	4	

ACICLOVIR					Layer 3 of 17
Nervous system disorders	Headache	21	0	18	
	Migraine	1	0	1	
	Amnesia	3	0	2	
	Disturbance in attention	1	0	1	
	Choreoathetosis	1	0	1	
	Paralysis	2	0	1	
	Tremor	5	0	4	
	Hyperreflexia	1	0	0	
	Ataxia	2	0	2	
	Coma	3	0	2	
	Consciousness fluctuating	2	0	1	
	Somnolence	3	0	3	
	Stupor	1	0	1	
	Syncope	3	0	3	
	Dizziness	12	0	10	
	Myoclonus	1	0	0	
	Hyperaesthesia	1	0	1	
	Paraesthesia	10	0	8	
	Dysgeusia	2	0	2	
	Hypoaesthesia	1	0	1	
	Speech disorder	1	0	0	
	Hypotonia	1	0	0	
	Neuropathy peripheral	1	0	0	
	Grand mal convulsion	1	0	1	
	Convulsion	5	0	3	
Pregnancy, puerperium and perinatal conditions	Intra-uterine death	2	0	1	
	Polyhydramnios	1	0	0	
Psychiatric disorders	Agitation	8	0	7	
	Anxiety	2	0	1	
	Nervousness	1	0	1	
	Fear	1	0	1	
	Confusional state	23	0	14	
	Disorientation	1	0	0	
	Delirium	1	0	0	
	Depression	5	0	4	

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ACICLOVIR					Layer 3 of 17
Psychiatric disorders	Delusion	1	0	1	
	Hallucination	28	0	19	
	Thinking abnormal	2	0	2	
	Mania	2	0	2	
	Euphoric mood	2	0	2	
	Aggression	2	0	2	
	Paranoia	3	0	3	
	Psychotic disorder	2	0	1	
	Insomnia	4	0	3	
	Abnormal dreams	1	0	1	
	Nightmare	1	0	1	
	Suicide attempt	1	0	1	
Renal and urinary disorders	Nephritis interstitial	1	0	0	
	Nephropathy toxic	7	0	7	
	Oliguria	1	0	0	
	Renal failure	2	0	0	
	Renal failure acute	16	0	10	
	Renal impairment	25	1	15	
	Pollakiuria	2	0	0	
	Urinary hesitation	1	0	1	
	Urinary retention	2	0	2	
	Glycosuria	1	0	1	
	Haematuria	4	0	1	
	Polyuria	1	0	1	
	Renal pain	3	0	1	
	Nephrolithiasis	2	0	0	
	Calculus bladder	1	0	0	
Reproductive system and breast disorders	Breast enlargement	1	0	0	
	Gynaecomastia	1	1	0	
	Breast pain	3	1	2	
	Menstrual disorder	1	0	0	
	Metrorrhagia	1	0	0	
	Oedema genital	1	0	1	
	Uterine haemorrhage	4	0	4	
Respiratory, thoracic and mediastinal disorders	Bronchospasm	5	0	2	

ACICLOVIR					Layer 3 of 17
Respiratory, thoracic and mediastinal disorders	Lung infiltration	1	0	0	
	Pleural effusion	1	0	0	
	Dyspnoea	7	0	3	
	Hyperventilation	1	0	0	
	Respiratory depression	1	0	0	
	Hypoxia	1	1	0	
	Respiratory disorder	1	0	1	
	Dysphonia	1	0	1	
	Pharyngolaryngeal pain	2	0	2	
	Throat tightness	1	0	1	
	Laryngeal oedema	1	0	1	
Skin and subcutaneous tissue disorders	Angioedema	4	0	4	
	Periorbital oedema	8	0	6	
	Urticaria	16	0	11	
	Blister	3	0	3	
	Dermatitis bullous	7	0	6	
	Stevens-Johnson syndrome	1	0	0	
	Skin necrosis	1	0	1	
	Swelling face	1	0	1	
	Rash erythematous	15	0	4	
	Red man syndrome	1	0	0	
	Skin exfoliation	1	0	1	
	Pityriasis rosea	1	0	1	
	Photosensitivity reaction	1	0	0	
	Pruritus	23	0	12	
	Rash pruritic	2	0	0	
	Psoriasis	1	0	1	
	Rash	33	0	20	
	Rash macular	1	0	0	
	Rash maculo-papular	23	1	4	
	Rash vesicular	2	0	1	
	Lipodystrophy acquired	11	0	0	
	Acne	2	0	1	
	Alopecia	6	0	4	
	Cold sweat	1	0	0	

Skin and subcutaneous tissue disorders	Hyperhidrosis	4	0	3
	Petechiae	1	0	0
	Purpura	3	0	2
Surgical and medical procedures	Drug therapy changed	1	0	1
Vascular disorders	Hypotension	5	0	3
	Thrombophlebitis	3	0	3
	Flushing	5	0	4
	Pallor	2	0	1
	Haemorrhage	1	0	1
	Hypertension	1	0	0

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ACICLOVIR — Layer 4 of 17

		ALL REPORT DATES		
		Causality Unclear Excluded		
		Total	Death Outcome	Sole Suspected
- Cases Including Medicine		241	8	96
- Occurrences of Medicine		248	8	96
- Reactions Related to Medicine		479	14	190
Blood and lymphatic system disorders	Anaemia	1	0	0
	Hypochromic anaemia	1	0	1
	Pancytopenia	2	0	0
	Coombs positive haemolytic a	1	0	0
	Haemolysis	1	0	0
	Thrombocytopenia	6	0	1
	Eosinophilia	1	0	0
	Leukopenia	2	0	0
	Neutropenia	8	0	0
Cardiac disorders	Atrioventricular block	1	0	1
	Extrasystoles	2	0	0
	Tachycardia	2	0	1
	Supraventricular tachycardia	1	0	0
	Cardiac arrest	1	1	1
	Cyanosis	1	0	0
	Palpitations	1	0	0
	Left ventricular failure	1	0	0
	Cardiomyopathy	1	0	0
Congenital, familial and genetic disorders	Multiple congenital abnormalit	2	0	0
Ear and labyrinth disorders	Deafness	1	0	0
	Tinnitus	2	0	0
	Vertigo	2	0	2
Eye disorders	Mydriasis	1	0	0
	Photophobia	3	0	1
	Diplopia	1	0	0
	Visual disturbance	2	0	1
Gastrointestinal disorders	Pancreatitis acute	1	0	0
	Rectal haemorrhage	1	0	1

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ACICLOVIR					Layer 4 of 17
Gastrointestinal disorders	Colitis	1	0	1	
	Oesophagitis	1	0	0	
	Diarrhoea	4	0	4	
	Abdominal pain	7	1	0	
	Dysphagia	1	0	0	
	Nausea	15	0	8	
	Vomiting	10	0	4	
	Steatorrhoea	1	0	0	
	Aphthous stomatitis	1	0	1	
	Mouth ulceration	1	0	0	
	Stomatitis	1	0	1	
	Ascites	1	0	0	
	Salivary hypersecretion	1	0	1	
	Salivary gland enlargement	1	0	0	
	Glossitis	1	0	1	
	Tongue oedema	2	0	1	
General disorders and administration site conditions	Application site reaction	1	0	0	
	Infusion site vesicles	1	0	0	
	Injection site extravasation	1	0	1	
	Injection site reaction	8	0	8	
	Chills	2	0	1	
	Pyrexia	13	0	4	
	Death	1	1	1	
	Sudden death	1	1	0	
	Fatigue	4	0	2	
	Malaise	4	0	2	
	Gait disturbance	1	0	1	
	Thirst	1	0	1	
	Ulcer	1	0	1	
	Face oedema	5	0	3	
	Oedema peripheral	2	0	1	
	Discomfort	1	0	1	
	Pain	2	0	2	
	Drug ineffective	1	0	1	
	Therapeutic response decrea	1	0	1	

ACICLOVIR					Layer 4 of 17
Hepatobiliary disorders	Hepatitis cholestatic	2	0	0	
	Jaundice	1	0	0	
	Hepatic function abnormal	12	1	2	
	Hepatic failure	2	1	0	
	Hepatic steatosis	2	0	0	
	Hepatitis	2	0	0	
Immune system disorders	Hypersensitivity	1	0	0	
	Anaphylactoid reaction	1	0	0	
Infections and infestations	Candidiasis	1	0	0	
	Pneumonia	1	0	0	
	Sepsis	2	1	0	
	Varicella	1	0	1	
Investigations	Blood creatine phosphokinase	1	0	0	
	Red blood cell sedimentation	1	0	1	
	Liver function test abnormal	1	0	0	
	Weight decreased	1	0	0	
	Blood creatinine increased	7	0	5	
	Blood urea increased	1	0	1	
	Drug level decreased	1	0	0	
Metabolism and nutrition disorders	Lactic acidosis	1	1	0	
	Acidosis	1	0	0	
	Anorexia	2	0	0	
	Hypokalaemia	1	0	0	
	Hyponatraemia	1	0	0	
	Diabetes mellitus	1	0	0	
	Hyperglycaemia	3	0	0	
	Hypoglycaemia	1	0	0	
	Hypercholesterolaemia	3	0	0	
	Hypertriglyceridaemia	4	0	0	
Musculoskeletal and connective tissue disorders	Arthritis	1	0	1	
	Arthropathy	1	0	0	
	Arthralgia	3	0	3	
	Osteoarthritis	1	0	0	
	Myalgia	5	1	4	
	Muscle atrophy	2	1	0	

ACICLOVIR					Layer 4 of 17
Musculoskeletal and connective tissue disorders	Myopathy	1	0	0	
	Back pain	1	0	0	
Neoplasms benign, malignant and unspecifi	Angiolipoma	1	0	0	
Nervous system disorders	IIIrd nerve paralysis	1	0	0	
	Encephalopathy	4	0	0	
	Headache	4	0	2	
	Disturbance in attention	1	0	1	
	Paralysis	2	0	1	
	Tremor	3	0	2	
	Hyperreflexia	1	0	0	
	Ataxia	2	0	2	
	Coma	2	0	1	
	Consciousness fluctuating	2	0	1	
	Somnolence	2	0	2	
	Syncope	1	0	1	
	Dizziness	4	0	3	
	Myoclonus	1	0	0	
	Paraesthesia	1	0	0	
	Speech disorder	1	0	0	
	Neuropathy peripheral	1	0	0	
	Grand mal convulsion	1	0	1	
	Convulsion	2	0	1	
Pregnancy, puerperium and perinatal condit	Polyhydramnios	1	0	0	
Psychiatric disorders	Agitation	3	0	2	
	Anxiety	1	0	0	
	Confusional state	12	0	7	
	Disorientation	1	0	0	
	Delirium	1	0	0	
	Depression	1	0	0	
	Delusion	1	0	1	
	Hallucination	18	0	11	
	Thinking abnormal	1	0	1	
	Paranoia	2	0	2	
	Insomnia	3	0	2	
Renal and urinary disorders	Nephritis interstitial	1	0	0	

ACICLOVIR					Layer 4 of 17
Renal and urinary disorders	Nephropathy toxic	7	0	7	
	Renal failure	2	0	0	
	Renal failure acute	13	0	7	
	Renal impairment	18	1	12	
	Pollakiuria	1	0	0	
	Haematuria	4	0	1	
	Polyuria	1	0	1	
	Renal pain	2	0	0	
	Nephrolithiasis	2	0	0	
	Calculus bladder	1	0	0	
Reproductive system and breast disorders	Breast enlargement	1	0	0	
	Gynaecomastia	1	1	0	
	Breast pain	1	1	0	
Respiratory, thoracic and mediastinal disorders	Bronchospasm	2	0	1	
	Lung infiltration	1	0	0	
	Pleural effusion	1	0	0	
	Dyspnoea	4	0	1	
	Hyperventilation	1	0	0	
	Respiratory depression	1	0	0	
	Hypoxia	1	1	0	
	Dysphonia	1	0	1	
	Throat tightness	1	0	1	
	Laryngeal oedema	1	0	1	
Skin and subcutaneous tissue disorders	Angioedema	1	0	1	
	Periorbital oedema	5	0	3	
	Urticaria	9	0	5	
	Blister	1	0	1	
	Stevens-Johnson syndrome	1	0	0	
	Skin necrosis	1	0	1	
	Rash erythematous	7	0	1	
	Red man syndrome	1	0	0	
	Pruritus	10	0	3	
	Rash pruritic	2	0	0	
	Psoriasis	1	0	1	
	Rash	14	0	4	

ACICLOVIR — Layer 4 of 17

Skin and subcutaneous tissue disorders	Rash macular	1	0	0
	Rash maculo-papular	16	0	2
	Rash vesicular	2	0	1
	Lipodystrophy acquired	11	0	0
	Acne	1	0	0
	Alopecia	3	0	1
	Cold sweat	1	0	0
	Hyperhidrosis	1	0	0
	Petechiae	1	0	0
	Purpura	2	0	1
Vascular disorders	Hypotension	5	0	3
	Thrombophlebitis	3	0	3
	Flushing	2	0	1
	Pallor	1	0	0
	Hypertension	1	0	0

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ACYCLO-V — Layer 5 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		6	4
- Occurrences of Medicine		6	4
- Reactions Related to Medicine		17	14
Cardiac disorders	Palpitations	1	1
	Myocardial infarction	1	0
Gastrointestinal disorders	Diarrhoea	1	0
	Nausea	1	1
General disorders and administration site conditions	Asthenia	1	1
	Malaise	1	1
	Oedema peripheral	1	1
	Drug ineffective	1	1
Metabolism and nutrition disorders	Hyperlipidaemia	1	0
Musculoskeletal and connective tissue disor	Arthralgia	1	1
Nervous system disorders	Dizziness	1	1
	Paraesthesia	1	1
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	1	1
	Pharyngolaryngeal pain	1	1
Skin and subcutaneous tissue disorders	Blister	1	1
	Pruritus	1	1
Vascular disorders	Pallor	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

Acihexal 5% — Layer 6 of 17

		ALL REF Causality Total
- Cases Including Medicine		1
- Occurrences of Medicine		1
- Reactions Related to Medicine		1
Gastrointestinal disorders	Lip blister	1

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

Blistex Antiviral Cold Sore Cream — Layer 7 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		1	1
- Occurrences of Medicine		1	1
- Reactions Related to Medicine		1	1
General disorders and administration site co	Application site oedema	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

GenRx Aciclovir — Layer 8 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		1	1
- Occurrences of Medicine		1	1
- Reactions Related to Medicine		1	1
General disorders and administration site co	Drug ineffective	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

Lovir — Layer 9 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		4	3
- Occurrences of Medicine		4	3
- Reactions Related to Medicine		5	4
Gastrointestinal disorders	Rectal haemorrhage	1	1
General disorders and administration site conditions	Drug ineffective	2	2
	Therapeutic response decrea	1	0
Surgical and medical procedures	Drug therapy changed	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ZOVIRAX — Layer 10 of 17

		ALL REPORT DATES		
		Causality Unclear Excluded		
		Total	Death Outcome	Sole Suspected
- Cases Including Medicine		200	1	152
- Occurrences of Medicine		202	1	152
- Reactions Related to Medicine		364	1	288
Blood and lymphatic system disorders	Thrombocytopenia	1	0	1
	Red blood cell abnormality	1	0	1
	Agranulocytosis	1	0	0
	Neutropenia	3	0	0
Cardiac disorders	Tachycardia	1	0	1
	Atrial fibrillation	1	0	1
	Palpitations	5	0	4
Ear and labyrinth disorders	Vertigo	1	0	1
Endocrine disorders	Inappropriate antidiuretic horr	1	0	1
	Hypothyroidism	1	0	0
Eye disorders	Conjunctivitis	2	0	2
	Keratitis	2	0	2
	Ulcerative keratitis	1	0	1
	Photophobia	2	0	1
	Visual disturbance	3	0	2
Gastrointestinal disorders	Diarrhoea	5	0	5
	Dyspepsia	2	0	2
	Abdominal pain	1	0	1
	Dysphagia	1	0	1
	Nausea	23	0	22
	Vomiting	14	0	12
	Cheilitis	1	0	1
	Stomatitis	1	0	1
	Dry mouth	2	0	2
	Glossitis	2	0	2
General disorders and administration site conditions	Application site reaction	10	0	10
	Injection site pain	1	0	1
	Injection site reaction	5	0	5

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ZOVIRAX					Layer 10 of 17
General disorders and administration site conditions	Pyrexia	1	0	0	
	Asthenia	1	0	1	
	Fatigue	2	0	1	
	Malaise	6	0	5	
	Gait disturbance	1	0	1	
	Face oedema	6	0	5	
	Oedema	1	0	0	
	Oedema peripheral	2	0	2	
	Chest pain	4	0	3	
	Pain	2	0	2	
	Drug ineffective	6	0	6	
	Therapeutic response decrea	1	0	1	
	Therapeutic response unexpe	2	0	1	
Hepatobiliary disorders	Jaundice	3	0	2	
	Hepatic function abnormal	10	0	4	
	Hepatitis	2	0	2	
	Hepatocellular injury	1	0	1	
Immune system disorders	Hypersensitivity	2	0	2	
Infections and infestations	Rash pustular	1	0	1	
	Pharyngitis	3	0	2	
Injury, poisoning and procedural complicatic	Medication error	1	0	1	
Investigations	Weight decreased	1	0	1	
	Crystal urine	1	0	1	
Metabolism and nutrition disorders	Anorexia	3	0	2	
	Hyponatraemia	3	0	2	
	Dehydration	1	0	1	
	Diabetes mellitus	1	0	1	
	Hyperglycaemia	1	0	1	
Musculoskeletal and connective tissue disorders	Arthritis	1	0	1	
	Arthralgia	1	0	1	
	Myalgia	5	0	5	
Neoplasms benign, malignant and unspecifi	Bladder cancer	1	0	0	
Nervous system disorders	Facial palsy	1	0	1	
	Encephalopathy	5	0	4	
	Headache	14	0	13	

ZOVIRAX					Layer 10 of 17
Nervous system disorders	Migraine	1	0	1	
	Amnesia	3	0	2	
	Choreoathetosis	1	0	1	
	Tremor	2	0	2	
	Coma	1	0	1	
	Somnolence	1	0	1	
	Stupor	1	0	1	
	Syncope	1	0	1	
	Dizziness	6	0	6	
	Paraesthesia	4	0	3	
	Dysgeusia	2	0	2	
	Hypotonia	1	0	0	
	Convulsion	3	0	2	
Pregnancy, puerperium and perinatal condit	Intra-uterine death	2	0	1	
Psychiatric disorders	Agitation	5	0	5	
	Anxiety	1	0	1	
	Nervousness	1	0	1	
	Fear	1	0	1	
	Confusional state	10	0	7	
	Depression	4	0	4	
	Hallucination	9	0	7	
	Thinking abnormal	1	0	1	
	Mania	2	0	2	
	Euphoric mood	2	0	2	
	Aggression	2	0	2	
	Psychotic disorder	1	0	0	
	Insomnia	1	0	1	
	Abnormal dreams	1	0	1	
	Nightmare	1	0	1	
	Suicide attempt	1	0	1	
Renal and urinary disorders	Nephritis interstitial	1	0	0	
	Oliguria	1	0	0	
	Renal failure acute	3	0	3	
	Renal impairment	8	0	3	
	Pollakiuria	1	0	0	

Renal and urinary disorders	Urinary hesitation	1	0	1
	Urinary retention	2	0	2
	Glycosuria	1	0	1
	Renal pain	1	0	1
Reproductive system and breast disorders	Breast pain	2	0	2
	Menstrual disorder	1	0	0
	Metrorrhagia	1	0	0
	Oedema genital	1	0	1
	Uterine haemorrhage	4	0	4
Respiratory, thoracic and mediastinal disorders	Bronchospasm	2	0	0
	Dyspnoea	3	0	2
	Pharyngolaryngeal pain	1	0	1
Skin and subcutaneous tissue disorders	Angioedema	3	0	3
	Periorbital oedema	3	0	3
	Urticaria	7	0	6
	Blister	1	0	1
	Dermatitis bullous	1	0	0
	Swelling face	1	0	1
	Rash erythematous	7	0	2
	Pityriasis rosea	1	0	1
	Photosensitivity reaction	1	0	0
	Pruritus	9	0	5
	Rash pruritic	1	0	0
	Rash	14	0	11
	Rash maculo-papular	7	1	2
	Acne	1	0	1
	Alopecia	3	0	3
	Hyperhidrosis	3	0	3
	Purpura	1	0	1
Vascular disorders	Flushing	3	0	3

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ZOVIRAX COLD SORE CREAM — Layer 11 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		37	36
- Occurrences of Medicine		37	36
- Reactions Related to Medicine		64	63
General disorders and administration site conditions	Application site reaction	26	26
	Face oedema	8	8
	Oedema	2	2
	Drug ineffective	7	6
Nervous system disorders	Headache	1	1
	Hyperaesthesia	1	1
	Paraesthesia	3	3
	Hypoaesthesia	1	1
Skin and subcutaneous tissue disorders	Dermatitis bullous	6	6
	Rash erythematous	1	1
	Skin exfoliation	1	1
	Pruritus	2	2
	Rash	4	4
Vascular disorders	Haemorrhage	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ZOVIRAX OPHTHALMIC OINTMENT — Layer 12 of 17

		ALL REPORT DATES	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		4	4
- Occurrences of Medicine		4	4
- Reactions Related to Medicine		5	5
Congenital, familial and genetic disorders	Cataract congenital	1	1
Eye disorders	Visual disturbance	1	1
General disorders and administration site co	Application site reaction	3	3

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

ZYCLIR — Layer 13 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		13	12
- Occurrences of Medicine		13	12
- Reactions Related to Medicine		23	21
Eye disorders	Accommodation disorder	1	1
Gastrointestinal disorders	Diarrhoea	1	1
	Nausea	1	1
	Vomiting	1	1
General disorders and administration site conditions	Malaise	2	2
	Pain	2	2
	Drug ineffective	2	2
Infections and infestations	Pharyngitis	1	1
Nervous system disorders	Headache	2	2
	Syncope	1	1
	Dizziness	1	0
	Paraesthesia	1	1
Psychiatric disorders	Confusional state	1	0
	Hallucination	1	1
	Paranoia	1	1
	Psychotic disorder	1	1
Respiratory, thoracic and mediastinal disord	Bronchospasm	1	1
Skin and subcutaneous tissue disorders	Pruritus	1	1
	Rash	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

FAMCICLOVIR					Layer 14 of 17
		ALL REPORT DATES			
		Causality Unclear Excluded			
		Total	Death Outcome	Sole Suspected	
- Cases Including Medicine		118	1	86	
- Occurrences of Medicine		119	1	86	
- Reactions Related to Medicine		246	10	175	
Blood and lymphatic system disorders	Thrombocytopenia	1	1	0	
	Eosinophilia	1	0	1	
Cardiac disorders	Bradycardia	2	0	0	
	Palpitations	2	0	0	
Ear and labyrinth disorders	Deafness	1	0	1	
	Tinnitus	1	0	1	
	Vertigo	1	0	1	
Endocrine disorders	Inappropriate antidiuretic horr	2	0	2	
	Hyperthyroidism	1	0	1	
Eye disorders	Visual disturbance	1	0	1	
Gastrointestinal disorders	Pancreatitis	1	0	1	
	Melaena	1	0	1	
	Diarrhoea	5	1	3	
	Dyspepsia	1	0	1	
	Faeces discoloured	1	0	1	
	Flatulence	1	0	1	
	Abdominal pain	7	0	5	
	Abdominal pain upper	1	0	1	
	Dysphagia	1	0	0	
	Nausea	18	0	14	
	Vomiting	12	0	9	
	Lip ulceration	1	0	1	
	Mouth ulceration	1	0	1	
General disorders and administration site conditions	Hypothermia	1	1	0	
	Pyrexia	2	0	1	
	Sudden death	1	1	0	
	Asthenia	1	0	1	
	Fatigue	7	0	6	

FAMCICLOVIR					Layer 14 of 17
General disorders and administration site conditions	Malaise	2	0	2	
	Chest discomfort	2	0	0	
	Influenza like illness	1	0	1	
	Face oedema	2	0	2	
	Oedema peripheral	1	0	1	
	Chest pain	1	0	0	
	Pain	1	0	1	
	Drug interaction	1	0	0	
	Therapeutic response decrea	1	0	0	
Hepatobiliary disorders	Jaundice	2	0	1	
	Hepatic function abnormal	5	0	2	
	Hepatitis	1	0	0	
Infections and infestations	Candidiasis	1	0	1	
	Hepatitis infectious	1	0	0	
	Sepsis	1	1	0	
	Herpes simplex	1	0	0	
	Herpes zoster	1	0	1	
	Oral herpes	1	0	1	
Injury, poisoning and procedural complications	Drug exposure during pregna	1	0	1	
	Fall	1	0	1	
	Medication error	1	0	1	
Investigations	International normalised ratio	1	0	0	
	Prothrombin level decreased	1	0	0	
	Liver function test abnormal	1	0	1	
	Weight decreased	1	0	0	
	Urine analysis abnormal	1	0	1	
Metabolism and nutrition disorders	Anorexia	3	0	2	
	Polydipsia	1	0	1	
	Hypokalaemia	1	0	1	
	Hyponatraemia	2	0	1	
	Dehydration	1	0	0	
	Alcohol intolerance	1	0	1	
	Diabetes mellitus	2	0	0	
	Gout	1	0	1	
Musculoskeletal and connective tissue disorders	Arthralgia	2	0	2	

FAMCICLOVIR					Layer 14 of 17
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0	1	
	Muscular weakness	1	0	1	
	Back pain	1	0	1	
Neoplasms benign, malignant and unspecifi	Testicular germ cell cancer	1	0	1	
Nervous system disorders	Encephalopathy	1	1	0	
	Headache	11	0	11	
	Migraine	1	0	1	
	Dementia	1	0	1	
	Memory impairment	1	0	0	
	Disturbance in attention	1	0	1	
	Paralysis	1	1	0	
	Ataxia	4	0	4	
	Coordination abnormal	1	0	1	
	Coma	1	0	1	
	Somnolence	1	0	1	
	Syncope	1	0	0	
	Dizziness	5	0	4	
	Paraesthesia	1	0	1	
	Dysgeusia	1	0	1	
	Hypoaesthesia	1	0	1	
	Post herpetic neuralgia	1	0	1	
	Dysarthria	2	0	2	
Pregnancy, puerperium and perinatal condit	Pre-eclampsia	1	0	1	
Psychiatric disorders	Anxiety	2	0	2	
	Nervousness	1	0	0	
	Confusional state	7	0	6	
	Disorientation	1	0	1	
	Delirium	1	0	1	
	Depression	3	0	3	
	Depersonalisation	1	0	1	
	Hallucination	6	0	5	
	Mental disorder	1	0	1	
	Insomnia	1	0	1	
Renal and urinary disorders	Nephritis interstitial	1	0	0	
	Renal failure acute	1	1	0	

Renal and urinary disorders	Renal impairment	3	0	0
	Dysuria	2	0	1
	Micturition disorder	1	0	0
	Urinary retention	2	1	1
	Choluria	1	0	1
	Nocturia	1	0	1
	Polyuria	1	0	1
Reproductive system and breast disorders	Premature menopause	1	0	1
	Atrophic vulvovaginitis	1	0	1
	Menstrual disorder	1	0	1
	Amenorrhoea	1	0	1
	Testicular disorder	1	0	1
Respiratory, thoracic and mediastinal disorders	Wheezing	1	0	1
	Pulmonary oedema	1	1	0
	Dyspnoea	1	0	1
	Cough	1	0	1
	Haemoptysis	1	0	1
Skin and subcutaneous tissue disorders	Angioedema	2	0	2
	Urticaria	4	0	2
	Lichenoid keratosis	1	0	1
	Erythema multiforme	1	0	1
	Stevens-Johnson syndrome	1	0	1
	Rash erythematous	1	0	1
	Photosensitivity reaction	1	0	1
	Pruritus	3	0	2
	Rash	8	0	6
	Rash maculo-papular	4	0	2
	Rash vesicular	1	0	0
	Hyperhidrosis	3	0	1
Vascular disorders	Thrombosis	1	0	0
	Flushing	1	0	1
	Hypertension	1	0	1
	Vasculitis	1	0	0

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

PENCICLOVIR — Layer 15 of 17

		ALL REPORT DATE!	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		3	2
- Occurrences of Medicine		3	2
- Reactions Related to Medicine		8	7
Gastrointestinal disorders	Lip oedema	1	1
	Tongue blistering	1	1
General disorders and administration site conditions	Application site reaction	1	1
	Chest pain	1	1
Infections and infestations	Herpes simplex	1	0
Musculoskeletal and connective tissue disor	Muscle spasms	1	1
Psychiatric disorders	Agitation	1	1
Respiratory, thoracic and mediastinal disord	Hyperventilation	1	1

THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

Nyal Cold Sore Cream — Layer 16 of 17

		ALL REPORT DATES	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		1	1
- Occurrences of Medicine		1	1
- Reactions Related to Medicine		1	1
Pregnancy, puerperium and perinatal condit	Abortion spontaneous	1	1

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THERAPEUTIC GOODS ADMINISTRATION
MEDICINE SUMMARY

Amcal Cold Sore Relief Tablet — Layer 17 of 17

		ALL REPORT DATES	
		Causality Unclear Exc	
		Total	Sole Suspected
- Cases Including Medicine		1	1
- Occurrences of Medicine		1	1
- Reactions Related to Medicine		3	3
Skin and subcutaneous tissue disorders	Urticaria	1	1
	Rash	1	1
Surgical and medical procedures	Drug therapy changed	1	1

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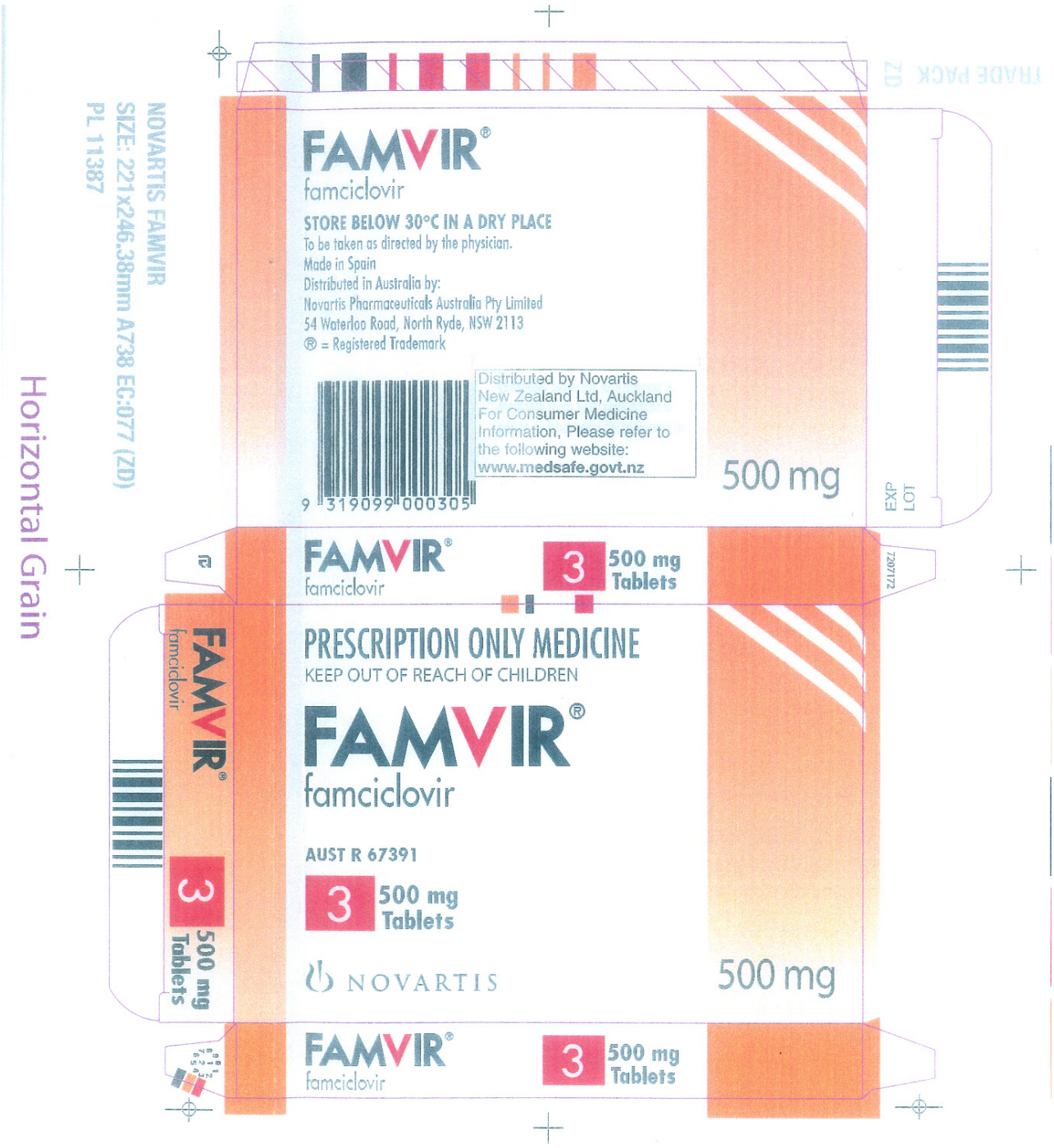
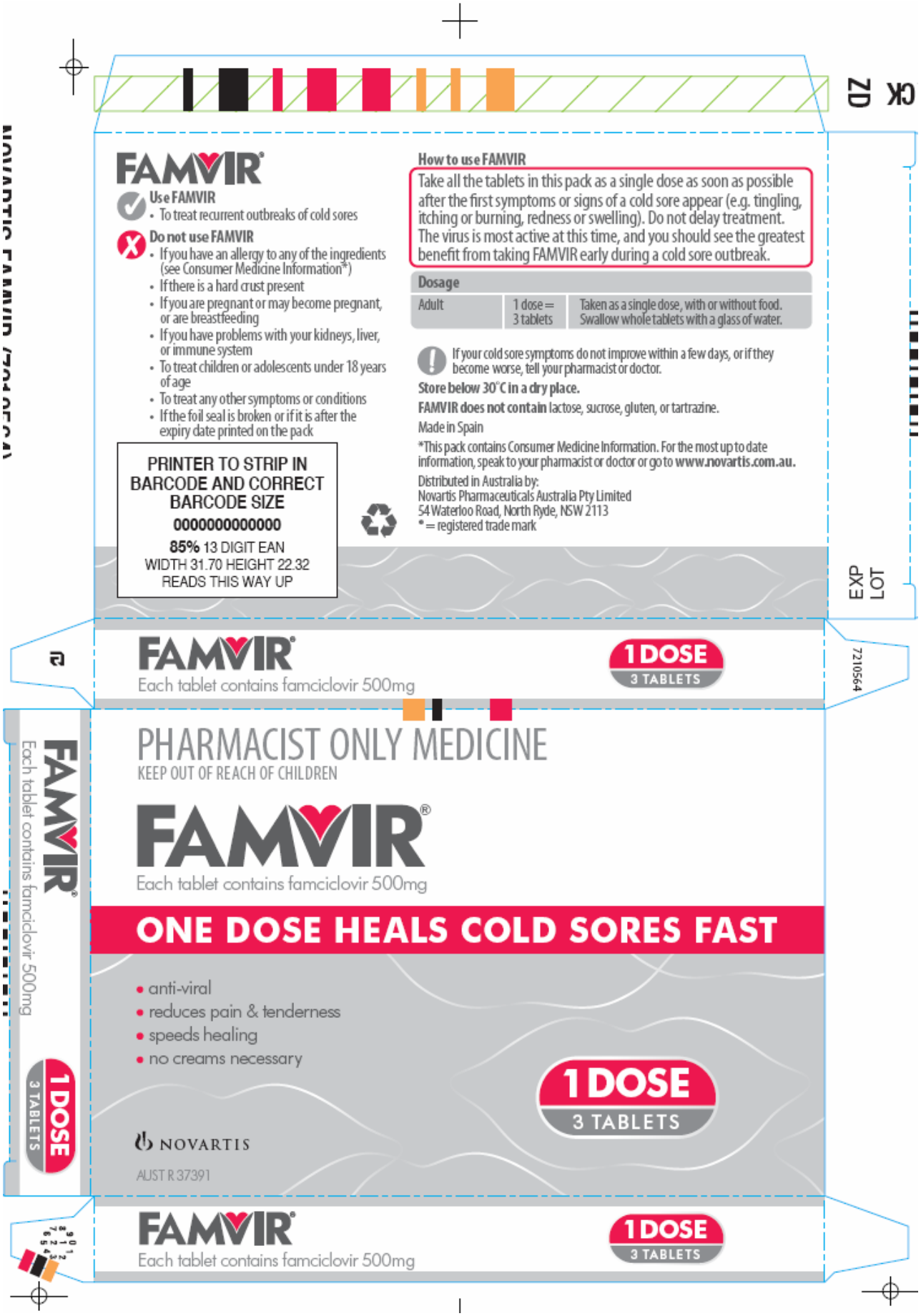
APPENDIX D – CURRENTLY APPROVED ARTWORK



APPENDIX E – DRAFT PROPOSED ARTWORK – PLEASE NOT THIS WILL BE REWORKED FOR NZ COMPLIANCE



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