SUBMISSION

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

   Penciclovir.

2. Proprietary name(s).

   Vectavir™.

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

   Orion Laboratories (NZ) Ltd
   PO Box 781 Whangaparaoa, New Zealand
   A wholly owned subsidiary of Orion Laboratories Pty Ltd t/a Perrigo Australia
   25-29 Delawney St, BALCATTA WA 6021, Australia

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

   Topical Cream 1%.

5. Pack size and other qualifications.

   2g in single pack cartonned tubes. VECTAVIR is a white homogenous cream for topical application.

6. Indications for which change is sought.

   For external use for the treatment of herpes labialis.

7. Present classification of the medicine.

   Prescription (non-topical).
   Pharmacy Only Medicine (topical only).

8. Classification sought.

   To harmonise with Australia Scheduling and amend topical penciclovir from Pharmacy Only to General Sales Medicine.

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

   Australia Schedule 4
   PENCICLOVIR except in preparations containing 1 per cent or less of penciclovir for the treatment of herpes labialis in packs containing 10 g or less (as of 1/10/17)

   UK, USA, Canada Topical Penciclovir: Pharmacy Only Medicine.

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute.

Original consent:

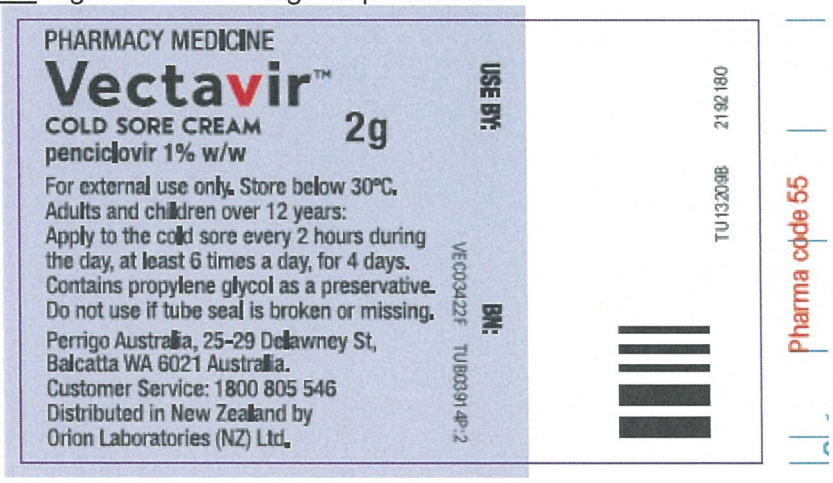
Vectavir Topical cream, 1% w/w, Cold Sore cream (Pharmacy only)	Penciclovir	Orion Laboratories (NZ) Ltd	Consent given	17/07/1997

Sales:

Sold-to party	Material	12 months sales quantity to May 2017
CDC Pharmaceuticals Ltd	Vectavir Cream 1% 2g	516
CDC Southern Branch	Vectavir Cream 1% 2g	36
CDC Napier	Vectavir Cream 1% 2g	24
CDC New Plymouth	Vectavir Cream 1% 2g	24
CDC WELLINGTON	Vectavir Cream 1% 2g	72
Green Cross Health Distribution Cen	Vectavir Cream 1% 2g	1,500
Pharmacy Wholesalers (BOP) Ltd	Vectavir Cream 1% 2g	324
ProPharma Wholesale	Vectavir Cream 1% 2g	204
Vantage Distribution Centre	Vectavir Cream 1% 2g	180

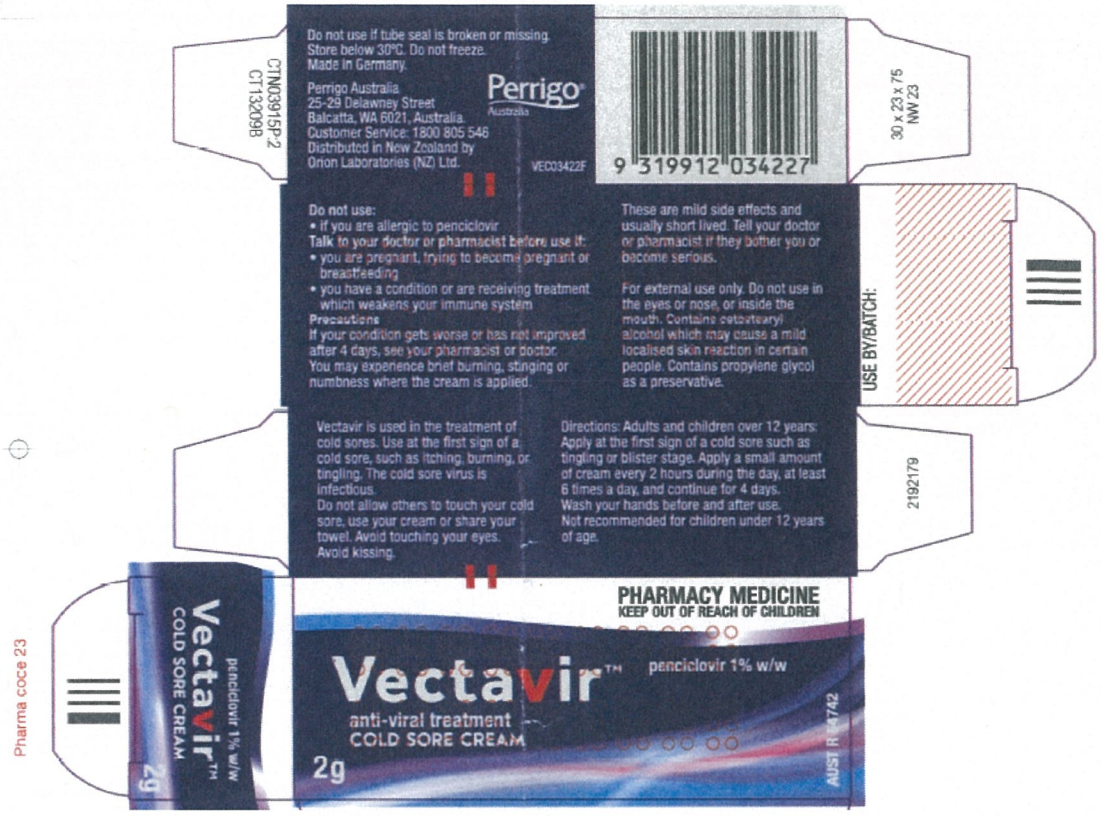
11. Labelling or draft labelling for the proposed new presentation(s).

Tube: 2g Tube containing 1% penciclovir



It is planned that with the reclassification "Pharmacy Medicine" would be removed. No other changes are planned.

Packaging: Labelled: Do not use if tube seal is broken or missing.



Note: Carton update currently pending approval. Updated carton, if approved, would be as above with "Made in Germany" removed.

It is planned that with the reclassification "Pharmacy Medicine" would be removed. No other changes are planned.

12. Proposed warning statements if applicable.

    Not applicable. There is little evidence that the pharmacy product has ever been used incorrectly, and no evidence to suggest that the unscheduled product would be used incorrectly either. With adequate and appropriate instructions on labelling and packaging, there is no need for any additional medical intervention or advice during the short time frame of use.

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

    Not applicable. Vectavir™ is the only topical penciclovir on the market currently in New Zealand. There is no intent to amend or include non-topical penciclovir in this application. It is intended that non-topical penciclovir products, usually injectable, remain as prescription only medicines, and would be unaffected by this change.

Part B

Reasons for requesting classification change including benefit - risk analysis.

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

   Harmonisation with recently approved Australian scheduling amendment. Public benefit of availability and greater choice in herpes labialis (cold sore) treatment with minimal side effects and public risk as demonstrated by long term Aciclovir availability as General Sales Medicine.

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

   None known, refer to Australian application Part 2.1 (A), page 11, for more detail regarding Risk/Benefits. The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indication.

   Regarding diagnosis without supervision, herpes labialis is a condition that has already been accepted as suitable for self-diagnosis. The availability of OTC aciclovir cream and other products for this indication provide reassurance that patients can diagnose herpes labialis without the aid of a physician/pharmacist. The small pack size (2g) means that it is unlikely to be used for other conditions such as herpes zoster. Refer to Australian application Part 1 - Overview, page 9, for more detail.

4. Relevant comparative data for like compounds.

   Topical aciclovir has been available as a General Sales Medicine long term without public issue. Allowing the same access for topical Penciclovir would allow greater public treatment choice and competition. Refer to Australian application Part 1 - Overview, page 9, and other Sections where relevant, for more detail.

5. Local data or special considerations relating to New Zealand.

   Topical Aciclovir is already a General Sales Medicine in New Zealand.

   The data for this medicine has already been evaluated in both Australia and New Zealand. This request is for harmonisation with Australia and to provide greater availability and public choice in the treatment of herpes labialis (cold sores).

6. Interactions with other medicines.

   The data for this medicine has already been evaluated and is well known. Aciclovir has been available for some time as a General Sale Medicine without issue and Penciclovir is not expected to differ. The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

7. Contraindications and precautions.

   The data for this medicine has already been evaluated and is well-known. The product is not known for misuse or abuse. Appropriate labelling and packaging

will manage any other risks, e.g. the product directions for use are restricted to children 12 years and over. There is a risk that younger children might take the product whilst in the home, but the likelihood of this risk is no different from the situation with any "Pharmacy Medicine". The standard label warning "Keep out of reach of children" will remain. The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

8. Possible resistance.

   The prevalence of aciclovir resistance in herpes simplex virus isolates from immunocompetent hosts has remained stable at approximately 0.3%. In immunocompromised patients, in whom the risk for developing resistance is much greater, the prevalence of resistant virus has also remained stable but at a higher level, typically 4 to 7%. Refer to Australia application Part 2.1 (F), page 15, for more detail and Part 2.1 (A), Page 11. The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

9. Adverse events - nature, frequency etc.

   Refer to Australian application Toxicity pages 10 & 12, and list of Australian AEs page 15 (refer table) and New Zealand below (refer table), accessed 17 Jun 2017 (10). The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

Detail for Penciclovir between 1 Jan 2000 and 31 Dec 2016
Number of reports for Penciclovir: 1

Number reports where death was reported: 0

Number of reactions: 1

Report	Date	Gender	Age	Medicine(s)	Reaction(s)
88376	Feb 2010	Male	0	Penciclovir topical (Suspect)	Nausea

10. Potential for abuse or misuse.

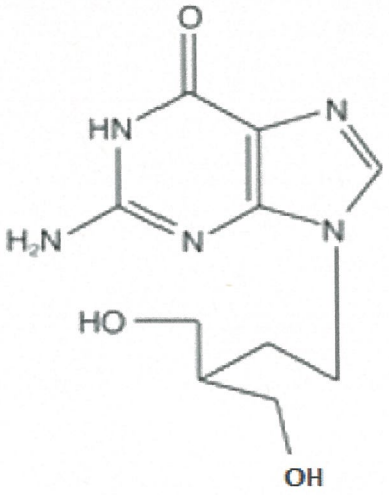
    Refer to Australian application Part 2.1 (E), page 14. The amendment from Pharmacy Only to General Sales Medicine will not result in any change of consequence in this category.

AUSTRALIAN APPLICATION

PART 1 – SUBSTANCE SUMMARY

Penciclovir, a synthetic guanine derivative, chemically designated as 9-[4-hydroxy-3-(hydroxymethyl)butyl] guanine. It is a white to pale yellow crystalline solid with a molecular weight of 253.3.

Chemical structure



Pharmacology

Penciclovir targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase). The triphosphate inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and therefore viral replication are inhibited (4). Penciclovir is only readily phosphorylated in virus-infected cells. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Accordingly, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir (4).

Two large patient initiated placebo controlled studies were conducted to determine the efficacy in treatment of recurrent herpes labialis. Patients included had a recurrence rate of three or more episodes per year. Treatment was to begin within one hour of the first sign or symptom and the cream was applied every 2 hours whilst awake for 4 days. The efficacy of treatment for periods longer than 4 days has not been assessed. Patients with a tendency not to develop classical lesions were excluded from the trials. In total 1516 patients were included in the penciclovir groups and 1541 patients in the placebo groups. (4).

Penciclovir 1% cream showed statistically significant benefits over placebo in time to healing ($p<0.004$), loss of lesion-associated pain ($p<0.0014$) and cessation of viral shedding ($p<0.0033$). Healing of lesions occurred up to one day earlier (approximately 30% faster) and the median duration of lesion associated pain was reduced by up to one day (25-30% faster) following penciclovir treatment compared to placebo. Patients receiving penciclovir ceased virus shedding one day earlier (approximately 40% faster) than placebo treated patients.
Results for the active triphosphate form show a long half-life of up to 10-20 hours, remaining active in infected cells for up to 12 hours, verifying the efficacy of penciclovir (2, 3). Although the directions for use recommend re-application every two hours during the day, at least six times a day, the 12-hour activity of the active substance results in significant concentrations remaining at night, which thereby continues to work without the need to re-apply while the consumer is asleep.

Toxicity
Both anti-viral agents, penciclovir and aciclovir, have a similar mechanism of action and also share a good safety profile with a long history of use. Penciclovir has minimal side effects with the majority of adverse effects being at the site of application including; erythema, itching and contact dermatitis (1, 3, 7). These side effects can be well managed by consumers through adequate and appropriate product labelling and packaging instructions.

It is noted that the safety profile of aciclovir and penciclovir are fundamentally similar and for more than 20 years aciclovir use has been considered safe and well tolerated regardless of the administration route. A good safety profile of penciclovir cream has been reported in two large clinical trials. Due to extremely low per-oral bioavailability penciclovir is poorly absorbed following oral administration. Systemic absorption is negligible and adverse effects are similar to those observed with placebo (1).
In the event of accidental oral ingestion or over-dosage, no untoward effects would be expected if the entire contents (2g) of penciclovir 1% cream were ingested and no specific treatment is necessary. Some irritation of the mouth could occur (4).

The range of uses of the substance
VECTAVIR (penciclovir 1% cream) is indicated for the treatment of recurrent cold sores (herpes labialis) in adults and children aged 12 years and over.
CAS number: 39809-25-1

OVERVIEW

It is estimated that up to one third of the world's population are affected by herpes simplex at some stage in their life, with the majority of infections presenting as repeated vesicular eruptions, herpes labialis within the general community (1). While herpes labialis is self-limiting and will generally resolve within 7-8 days, it can significantly decrease quality of life of those with active or recurrent infections as it can be painful, emotionally distressing and highly contagious (1,6). Historically, penciclovir has been used to treat herpes labialis topically, successfully promoting faster resolutions and a reduction in pain.

Topical cold sore treatments are commonly used by consumers after self-diagnoses of their condition, as already occurs with topical aciclovir. Penciclovir, an alternate option for recurrent cold sore sufferers, is in many respects similar to aciclovir, with benefits in improved healing time and associated pain (1, 4). As a major difference with aciclovir, available as a 5% topical formulation, penciclovir topical products are formulated at 1%, and although less concentrated they still retain an effective therapeutic outcome due to their greater activity, exclusive towards infected cells.

Penciclovir is indicated only for short term topical use. The product is intended to be applied at two hourly intervals, at least six times a day for up to four days as stated on labelling and packaging (4). The nature of the product indication is self-limiting. The mean duration of recurrences is 7–8 days, but individual episodes of up to 15 days have been reported (1). As for aciclovir, it has a low risk of masking a serious disease, compromising the medical management of a disease, or resulting in a consumer mistaking a cold sore for a more serious condition. With an indicated time frame for product use of 4 days, any misdiagnosis would not significantly delay any referral to a healthcare professional. In addition to an excellent well-defined safety profile, penciclovir is a topical application with no known risk of misuse and abuse; it has high selectivity to viral cells; and low bioavailability / toxicity to human cells, making this medicine a good candidate for reclassification in line with aciclovir topical products.

Reclassification of penciclovir topical would increase the availability of the product to the general community, and act as an alternative to aciclovir topical allowing consumers a greater freedom of choice. Reclassification would also be beneficial for immediate and early access to treatment, since penciclovir is effective at every stage of herpes labialis cycle, from tingle, to blister, providing potential for early symptom relief regardless of the stage of the condition (1, 6). With greater access and quicker healing, the virus will be less likely to be transmitted to others, potentially reducing spread and minimising frequency of occurrence (1).

Since aciclovir is no longer a scheduled product when used topically for herpes labialis, it would be logical for both penciclovir and aciclovir to be similarly scheduled and equally accessible to the consumer.

PART 2 – BODY OF THE APPLICATION

BACKGROUND

Current Scheduling status for Penciclovir:

Schedule 4 - PENCICLOVIR **except** when included in Schedule 2.
Schedule 2 - PENCICLOVIR for external use for the treatment of herpes labialis.

Penciclovir is a synthetic guanine analogue which has antiviral activity similar to aciclovir. It is active against herpes simplex 1 and 2 and also varicella-zoster, after the transcellular conversion of penciclovir to penciclovir triphosphate via virus induced thymidine kinases. Consequently, penciclovir triphosphate inhibits viral DNA polymerase and DNA synthesis for up to twelve hours in infected cells (2, 3, 4). Penciclovir, for external use in the treatment of herpes labialis, is currently listed as a Schedule 2, "Pharmacy Medicine". However, aciclovir, a similar anti-viral agent indicated for the same condition, was reclassified in 2002 from Schedule 2 to Unscheduled, on the basis that the product was safe, simple to use and increased access would be beneficial to the general public.

Additionally treatment of herpes labialis 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 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.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PART 4 OF THE POISONS STANDARD – SCHEDULING OR RESCHEDULING OF SUBSTANCES

(A) Risks and Benefits Associated with the Use of a Substance

Penciclovir and aciclovir have almost identical safety profiles and activity against herpes simplex virus (1). While there has been an increase in the use of anti-viral agents, both aciclovir and penciclovir, resistance has not become a problem in practice, due to resistance being the result of reduced thymidine kinase levels resulting in viruses with reduced pathogenicity relative to wild-type viruses (1, 4, 8),

with the majority of resistant viruses being reported in immunocompromised patients (1, 5, 8). Given that VECTAVIR (penciclovir 1% cream) is not indicated for the use in immunocompromised consumers, the risk of resistance in association with this product when used as per instructions is minimal.

Although penciclovir does have a good safety profile, topical use has been associated with application site reactions including; erythema, itching and contact dermatitis resulting in consumers experiencing uncomfortable side effects (1, 4).

Nevertheless, penciclovir has been studied to be efficacious in the treatment of recurrent cold sores. Studies have concluded that treatment of cold sores with penciclovir improve healing and duration of pain in immunocompetent participants (1, 4). Similarly, given that cold sores are extremely contagious prior to crusting, any improvement in healing aids in the prevention of spreading the virus. Unlike aciclovir, penciclovir applied from the prodromal phase, both reduced time to healing and duration of pain and is therefore more suitable for treatment at any stage of the condition (6). At present penciclovir is only available to be purchased in retail pharmacies as a "Pharmacy Medicine" medicine. Reclassification of penciclovir would allow the product to be more accessible to the community, provide an alternative treatment option and greater choice to consumers, without any added risk of side effects or safety issues, when compared to aciclovir.

(B) the purposes for which a substance is to be used and the extent of use of that substance

VECTAVIR (penciclovir 1% cream) is indicated for the treatment of recurrent cold sores (herpes labialis) in adults and children aged 12 years and over. This product was first registered in Australia in 1997. It has been available as a "Pharmacy Medicine," S2 in Australia under the trade name VECTAVIR since 2006 and was previously available as "Prescription Only" product, S4. VECTAVIR (penciclovir 1% cream) is an alternative for aciclovir (patented in 1979, FDA approved in1982, and has been used medically as a topical product since 1983).

(C) Toxicity and Safety of the Substance

Herpes labialis is easily recognisable to recurrent suffers, who are familiar with their condition and the signs and symptoms of new lesions. The earliest symptom of a cold sore, the tingling sensation is knowingly identifiable to consumers who are able to self-diagnose and treat the cold sore prior to the formation of a blister. Similarly, given the self-limiting nature of cold sores, which generally heal within 7 to 10 days, the potential for harm from inappropriate use is low (6).

As the symptoms of cold sores are specific and commonly known within the community they are unlikely to be confused with other more serious conditions or diseases. VECTAVIR (penciclovir 1% cream) would not be likely to mask symptoms or delay the diagnosis of a serious condition due to its short treatment recommendations of four days and the small packaging size of 2g. Any delay in diagnosis would be unlikely to affect prognosis.

The application of VECTAVIR (penciclovir 1% cream) is simple and convenient for consumers to competently adhere to. With adequate and appropriate instructions on labelling and packaging, there is no need for any additional medical intervention or advice during the short time frame of use. The product is intended to be applied at two hourly intervals, at least six times a day for up to four days as stated on labelling and packaging. Studies have found that the dose for the short term treatment of penciclovir 1% is effective and well tolerated (1, 4, 6). Given the high selectivity of penciclovir and its prodrug for infected cells and the negligible activity in uninfected cells, its low bioavailability, toxicity from ingestion is unlikely, including any likelihood to produce dependency, be misused, abused or illicitly used (1, 3, 8). For example, following application of VECTAVIR (penciclovir 1% cream) in a human volunteer

study at a daily dose of 180mg penciclovir (approximately 67 times the estimated usual clinical daily dose) to abraded and occluded skin for 4 days, penciclovir was not quantifiable in plasma and urine (4).

There have been three notified adverse reactions associated with the use of VECTAVIR (penciclovir 1% cream) to the TGA since 1997 (7). These adverse events include of reactions at the application site and associated swelling of the lips, for which the safety of the formulation excipients, (refer formulation below), is well established and the inclusion of penciclovir does not appear to alter their dermal safety profile (4). Nevertheless, there was one report of chest pain, muscle spasms and hyperventilation in conjunction with a reaction at the application site, but given the low bioavailability of the product, it is more likely that these effects were a result of anxiety due to the reaction as opposed to penciclovir systemic effects (7). Given that there have only been three adverse reports and the reactions have been mostly superficial, appropriate labelling and packaging can minimise risk and enable consumers to autonomously identify and manage the side effects appropriately.

(D) Dosage, Formulation, labelling, packaging and presentation of a Substance

Dosage:

VECTAVIR cream should be applied at approximately 2 hourly intervals during waking hours, at least 6 times per day, for 4 days, to ensure effective treatment.

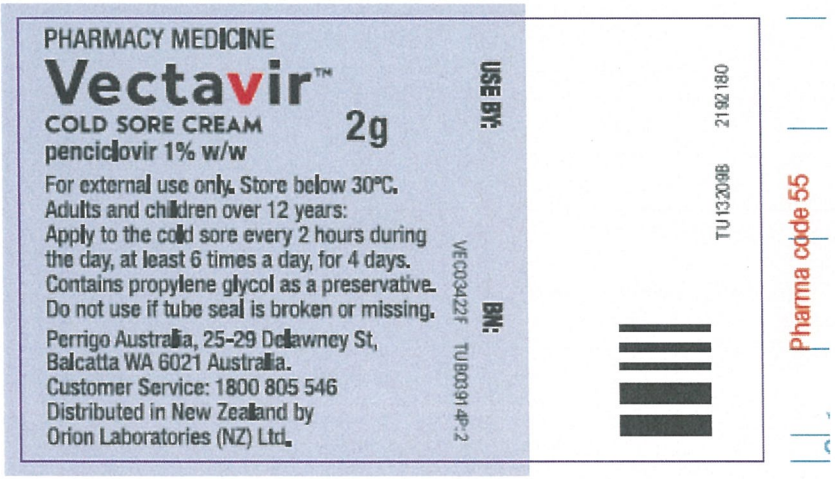
Formulation:

Penciclovir 1%

- Paraffin, Soft White
- Paraffin, Liquid
- Cetostearyl alcohol
- Propylene glycol
- Cetomacrogol 1000
- Water-purified.

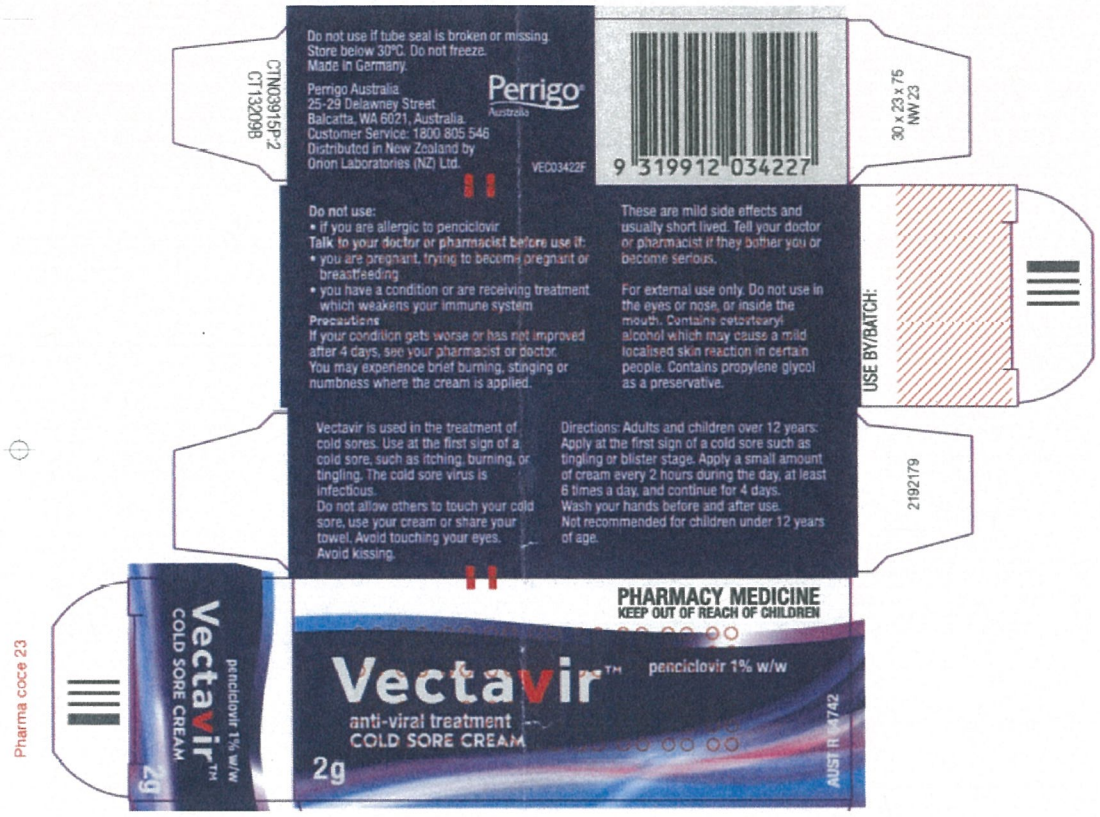
Labelling:

- Tube: 2g Tube containing 1% penciclovir



It is planned that with the reclassification "Pharmacy Medicine" would be removed. No other changes are planned.

- Packaging: Labelled: Do not use if tube seal is broken or missing.



It is planned that with the reclassification "Pharmacy Medicine" would be removed. No other changes are planned.

- Presentation: VECTAVIR is a white homogenous cream for topical application available as a 2g tube.

(E) Potential for Misuse/Abuse of the Substance

There does not appear to be any reports of overdose, misuse or abuse with penciclovir 1% cream. There is little evidence that the pharmacy product has ever been used incorrectly, and no evidence to suggest that the unscheduled product would be used incorrectly. Penciclovir is not considered a drug of abuse or addiction. The potential for abuse, misuse or overdose is low due to minimal systemic absorption. For example, following application of VECTAVIR (penciclovir 1% cream) in a human volunteer study at a daily dose of 180mg penciclovir (approximately 67 times the estimated usual clinical daily dose) to abraded and occluded skin for 4 days, penciclovir was not quantifiable in plasma and urine (4).

Regarding diagnosis without supervision, herpes labialis is a condition that has already been accepted as suitable for self-diagnosis. The availability of OTC aciclovir cream and other products for this indication provide reassurance that patients can diagnose herpes labialis without the aid of a physician/pharmacist. The small pack size (2g) means that it is unlikely to be used for other conditions such as herpes zoster.

Refer DAEN Report below, accessed 10 Aug 2016, review period 1/1971-4/2016 (7).

Case number[i]	Report entry date[ii]	Age (yrs)[iii]	Gender[iv]	Medicines reported as being taken[v]	MedDRA reaction terms[vi]
121961	28/10/1997	-	F	• LPV (Phenoxymethylpenicillin) - Suspected • Vectavir (Penciclovir) - Suspected	• Herpes simplex
126593	09/04/1998	-	M	• Vectavir (Penciclovir) - Suspected	• Agitation • Application site reaction • Chest pain • Hyperventilation • Muscle spasms
233011	04/09/2007	-	F	• Vectavir (Penciclovir) - Suspected	• Lip oedema • Tongue blistering

The product directions for use are restricted to children 12 years and over. There is a risk that younger children might take the product whilst in the home, but this is no different from the situation with any "Pharmacy Medicine". The standard label warning "Keep out of reach of children" will remain.

Appropriate labelling and packaging will manage any risks.

(F) Any Other Matter that May be Relevant to the Scheduling of a Substance

Penciclovir is structurally similar to aciclovir thus; these two anti-viral agents exhibit similar mechanisms of actions and side effects. It is important to note that aciclovir in preparations containing 5 per cent or less, for the treatment of herpes labialis in packs of 10 g or less is currently unscheduled. The proposed reclassification of penciclovir is at a lower strength of 1% and a lower quantity size of 2g compared to aciclovir.

A review of herpes simplex virus resistance to aciclovir and penciclovir after two decades of antiviral therapy states that "In spite of the distribution of over 2.3×10^6 kg of these nucleoside analogues, the prevalence of aciclovir resistance in herpes simplex virus isolates from immunocompetent hosts has remained stable at approximately 0.3%. In immunocompromised patients, in whom the risk for developing resistance is much greater, the prevalence of resistant virus has also remained stable but at a higher level, typically 4 to 7% (8). Therefore there does not appear to be any signs of increased viral resistance as a result of the current use of penciclovir/aciclovir, nor is there expected to be any increase in resistance when penciclovir is granted the same level of community access as aciclovir.

A study conducted by Femiano (6) compared the efficacy of aciclovir and penciclovir. The findings of this study demonstrated the possible superiority of penciclovir due to its better penetration. Femiano's study found that in the aciclovir took 6 days for lesions to form a crust and 5 days for the pain to subside compared to penciclovir which took 4 days for both the formation of a crust and a reduction in pain. Therefore, penciclovir has the potential to improve the outcomes of cold sore suffers and reduce the risk of transmission to other members of the community.

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

(A) Risks and Benefits Associated with the Use of a Substance

Please refer to Part 2.1(a), "Risks and Benefits Associated with the Use of a Substance."

(B) the purposes for which a substance is to be used and the extent of use of that substance

Please refer to Part 2.1(b), "The purposes for which a substance is to be used and the extent of use of that substance."

(C) Toxicity and Safety of the Substance

Please refer to Part 2.1(c), "Toxicity and safety of the substance."

(D) Dosage, Formulation, labelling, packaging and presentation of a Substance

Please refer to Part 2.1(d), "Dosage, formulation, labelling, packaging and presentation of a substance."

(E) Potential for Misuse/Abuse of the Substance

Please refer to Part 2.1(e), "Potential for misuse/abuse of the substance."

(F) Any Other Matter that May be Relevant to the Scheduling of a Substance

Please refer to Part 2.1(f), "Any other matter that may be relevant to the scheduling of a substance.".

PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

In Decision 2001/33 – 12 November 2001, the Committee agreed to amend the SUSDP to exempt dermal preparations containing aciclovir for use in the treatment of herpes labialis (cold sores) from the requirements of scheduling. This decision was made on the basis that the product meets the criteria for a suitable indication for an unscheduled product, and the condition being treated is short-term, self-limited and appropriate for self-diagnosis and management. In addition, the product is simple to use and increasing the access to such a product would be beneficial to public health.

Due to the close similarities in mode of action, safety, toxicity, ease-of-use, indications, appropriateness and benefit to public health, penciclovir meets the same criteria as the supporting data used by aciclovir reclassification. For this reason the past scheduling decision details have been included in Supporting Data Details.

SUPPORTING DATA DETAILS

Past Scheduling Decisions for Aciclovir:

DECISION 2001/33 - 12.

The Committee agreed to amend the SUSDP to exempt dermal preparations containing aciclovir for use in the treatment of *herpes labialis* (cold sores) from the requirements of scheduling. This decision was made on the basis that the product meets the criteria for a suitable indication for an unscheduled product, and the condition being treated is short-term, self-limited and appropriate for self-diagnosis and management. In addition, the product is simple to use and increasing the access to such a product would be beneficial to public health.

National Drugs and Poisons Schedule Committee

Record of the Reasons of Meeting 34 - **23 February 2002**
Schedule 2 – Amendment
ACICLOVIR – delete entry.

Schedule 4 – Amendment
ACICLOVIR – amend entry to read:
ACICLOVIR except in preparations containing 5 per cent or less of aciclovir for the treatment of Herpes labialis in packs containing 10 g or less.

The Committee reconsidered the Schedule 2 amendment for aciclovir made at the November 2001 meeting.

BACKGROUND

National Drugs and Poisons Schedule Committee

Record of the Reasons of Meeting 34 - February 2002 20

The November 2001 NDPSC Meeting agreed to exempt from the requirements of scheduling, preparations containing 5% or less of aciclovir for the treatment of *Herpes labialis* in a pack size of 10 g or less. The Xxxxxx xxxx, Xxxxxx xxxx and Xxxxxx xxxx, provided November 2001 pre-meeting submissions, supporting the retention in S2 of preparations containing 5% or less of aciclovir for the treatment of Herpes simplex virus (HSV). Xxxxxx xxxx and Xxxxxx xxxx had based their argument on the rationale that professional intervention was essential to reduce the potential for inappropriate and ineffective use of the product and exempting it would increase the risk of resistance development as a consequence of indiscriminate use. Xxxxxx xxxx had also argued that treatment of HSV involved a degree of complexity, which highlighted the need for access to professional advice/counselling for quality use. Post-meeting comments were received from Xxxxxx xxxx, Xxxxxx xxxx and Xxxxxx xxxx, reiterating their position that products containing 5% or less aciclovir for the treatment of *Herpes labialis*, in a pack size of 10 g or less, should be retained as S2 medicines.

DISCUSSION
The Committee noted the post- November 2001 meeting comments from Xxxxxx xxxx, Xxxxxx xxxx and Xxxxxx xxxx, The Committee noted that Xxxxxx xxxx had highlighted the following points:

- The arguments made by the applicant to address the issue of abuse potential, specifically related to the pack size of 2 g. Subsequent exemption of preparations containing 5% or less aciclovir for the treatment of *Herpes labialis* allowed for a pack size of 10 g, which was a considerable increase in quantity and by itself could induce inappropriate use.
- Use of products for the treatment of HSV involved a complex regimen, and access to professional advice was necessary to minimise the potential for inappropriate use. The Committee noted that Xxxxxx xxxx had highlighted the following points:
- The long history of safe use of the product was partly attributable to its proximity to professional advice, as a pharmacy-only medicine. It was stated that while the proposed exemption applied to aciclovir for the treatment of *Herpes labialis*, aciclovir was also marketed as ophthalmic ointment, in the same pack size and strength as the cold sore product. It was suggested that consumers were unlikely to be able to differentiate between the use of two products with similar same pack size and strength.
- Increasing product availability could lead to the development of resistance due to less judicious use, and in addition, use of topical antiviral agents was not generally recommended by the *Therapeutic Guidelines* (Antibiotic).

The Committee noted that Xxxxxx xxxx had raised the following points:

- Dermal preparations containing 5% or less of aciclovir for the treatment of cold sores were appropriately listed as S2 poison, as per the AHMAC *Guidelines for the NDPSC,* and argued that there were no criteria in the Guidelines for unscheduled products.
- Community pharmacists' anecdotal experience suggested that the general public was not always able to correctly self-diagnose symptoms of cold sores without the assistance of a health professional. This finding was demonstrated in a study conducted in 1999 by the Xxxxxx xxxx, where pharmacists had cited examples of consumers misdiagnosing melanoma as cold sores.
- The combination of exemption of topical aciclovir in pack sizes of up to 10g, and advertisement of broader indications for Xxxxxx xxxx on the Internet, including use in the treatment of genital herpes, may promote unapproved uses of this product in Australia. Additionally, the supply of larger quantities (ie, 10 g) would have the potential to delay treatment should the condition be mis(self)-diagnosed.
- The November 2001 consideration did not address the issue of efficacy of individual topical aciclovir formulations, such as those containing polyethylene glycol (PEG), where sensitivity of some consumers may be an issue.
- The survey conducted by the Xxxxxx xxxx in January 2002 did not support the Committee's contention of wide availability overseas and its lack of concern over the potential for resistance development.
- The Committee also noted that correspondence from the Xxxxxx xxxx had been included in the Xxxxxx xxxx submission, indicating support for the retention of topical aciclovir in S2.
- The Committee recalled that the evaluation report submitted to the November 2001
- NDPSC meeting had stated that:

The indication, *Herpes simplex* virus infections of the lips and face (*Herpes labialis* or cold sores), met the criteria for a suitable indication for an unscheduled product. *Herpes labialis* is a short-term, self-limited condition, often self-treated and unlikely to be misdiagnosed by the consumer. In addition, the product was simple to use even in the absence of advice or counselling.

- Early treatment suggested better response to aciclovir indicating that wider availability of such a product would be beneficial to public health.
- There were no public health concerns in relation to any criteria listed in the NDPSC Guidelines with regard to Xxxxxx xxxx and its wide availability overseas had shown no evidence of viral resistance.
- It was recommended that the entry for aciclovir be amended to exempt preparations containing 5% or less of aciclovir for dermal use in a pack size of 2g or less.

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The Committee considered the following issues raised by its members:

- Therapeutic products including idoxuridine dermal preparations containing 0.5% idoxuridine for the treatment of cold sores, and other antiviral products had been available in supermarkets for a long time. On this basis, it would be appropriate for 5% aciclovir dermal preparations to be given similar availability as idoxuridine, for consistency.
- *Herpes labialis* is a self-limiting condition, easily self-diagnosed by consumers and dermal products containing 5% aciclovir for the treatment of such a condition was unlikely to cause adverse effects, even if misused. Whilst the

potential to misdiagnose skin cancer as cold sores was a valid concern, there was no indication that this was a statistically significant occurrence. Additionally, the short duration of treatment, i.e. 5 days, and appropriate product labelling (eg, "If symptoms do not improve after 5 days, see your doctor") should safely address concerns of this nature.

- The potential to confuse aciclovir cold sore preparations with the ophthalmic preparations could also be resolved with appropriate product labelling.
- The potential health benefits to be gained by increasing access to an efficacious medicine to assist in the early treatment of cold sore symptoms outweighed the potential risks associated with the product.
- The Xxxxxx xxxx submission disputed the claim in the evaluation report that Xxxxxx xxxx had 'wide availability overseas'. Xxxxxx xxxx stated that countries including Sweden, Netherlands, UK, US, Denmark and Ireland, marketed this product as OTC medicine, not as 'general sale'. A Member responded that whilst Xxxxxx xxxx had been available in proximity to advice by health professionals in some countries, the evidence available had not altered the product's long history of safe use, in the context of considerable post-marketing experience.
- The issue of development of viral resistance had been addressed at the November 2001 meeting and no new studies relating to this concern had been provided, particularly in relation to immuno-competent individuals.
- Retention of the 10 g pack size restriction on exempt products containing 5% or less aciclovir for the treatment of cold sores was considered appropriate to minimise regulatory impact on currently registered products.

DECISION 2002/34 - 13.

The Committee confirmed that Decision 2001/33-12 from the November 2001 meeting, exempting 5% or less aciclovir for the treatment of *Herpes labialis* in pack sizes of 10 g or less, remains appropriate. This decision was based on the grounds that *Herpes labialis* is a short-term and self-limiting condition, and appropriate for self-diagnosis and management by consumers. In addition, the product is simple to use and increasing access to such a product would be beneficial to public health.

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Schedule 2 – Amendment
ACICLOVIR – delete entry.
Schedule 4 – Amendment
ACICLOVIR – amend entry to read:
ACICLOVIR **except** in preparations containing 5 per cent or less of aciclovir for the treatment of *Herpes labialis* in packs containing 10 g or less.

COPIES OF PAPERS REFERENCED

As attached.

PART 4 – BIBLIOGRAPHY

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5. Sarisky R, Profiling penciclovir susceptibility and prevalence of resistance of herpes simplex virus isolates across eleven clinical trials, Arch Virol 2003 148: 1757–1769.
6. Femiano F, Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with aciclovir, Oral Diseases 2001; 7:31–33.
7. DAEN_Penciclovir 201608.pdf
8. Bacon T Herpes Simplex Virus Resistance to Acyclovir and Penciclovir after Two Decades of Antiviral Therapy ASM 2016.
9. Current ARTG

PART 5 – NZ BIBLIOGRAPHY

10. Medsafe AEs Report for Penciclovir - Suspected Medicine Adverse Reaction Search (SMARS) accessed 12 June 2017.