Public Assessment Report

Fenistil Cold Sore Cream

PL 00030/0215

Novartis, Consumer Health

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Lay Summary

The Medicines and Healthcare products Regulatory Agency (MHRA) assessed a National simple abridged application in association with a reclassification application and granted a Marketing Authorisation (licence) to Novartis Consumer Health for the medicinal product Fenistil Cold Sore Cream (PL 00030/0215) on 24th August 2006.

After consideration by the Committee on Safety of Medicines (CSM) and an external consultation exercise, the legal status of Fenistil Cold Sore Cream was altered from Prescription Only Medicine to Pharmacy Only. This will allow pharmacists to dispense Fenistil without a prescription from a physician. Fenistil Cold Sore Cream contains the active ingredient penciclovir and is used for the treatment of herpes simplex virus infections of the lips and face (herpes labialis or cold sores) in adults and children over 12 years of age.

Scientific Discussion

Introduction

This Public Assessment report is for Fenistil Cold Sore Cream and is based on the reports for a National simple abridged application in association with a reclassification application (Prescription Only Medicine (POM) to Pharmacy (P)) for Fenistil Cold Sore Cream (PL 00030/0215). The reference product is Vectavir Cold Sore Cream (PL 00030/0210). Fenistil Cold Sore Cream (containing penciclovir 10mg/g), is for the treatment of cold sores (herpes labialis) in persons over 12 years. The applications were submitted by Novartis Consumer Health.

Penciclovir is an antiviral drug, which is used either topically or parenterally. Penciclovir 1% cream was first authorised in the UK in 1996, for the treatment of cold sores. The product has POM legal status in the UK.

Aciclovir, an antiviral similar to penciclovir, has been available without prescription in the UK since 1993, and was switched from P to GSL in June 2004. Apart from aciclovir, there are several other OTC products already available for the relief of cold sores. These typically contain one or more ingredients of the following types: local anaesthetics; analgesics; antiseptics; astringents.

PROPOSED CHANGES

It was proposed that the P product will be identical to the POM product, apart from a different product name and the introduction of a maximum pack size of 2g. The proposed indication is the same as for the POM product, *the treatment of cold sores (herpes labialis), in adults and children over 12 years of age.*

The EC Directive on the *Community Code relating to Medicinal Products for Human Use* (2001/83/EC as amended) classifies medicines into those subject to medical prescription and those not subject to prescription control. These criteria have been incorporated into section 58A of the Medicines Act. Prescription control is required for medicines which meet the following criteria:

a direct or indirect danger exists to human health, even when used correctly, if utilised without medical supervision
there is frequent incorrect use which could lead to a direct or indirect danger to human health
contain a substance the activity and/or the side effects of which require further investigation
are normally prescribed by a doctor to be administered parenterally.

This assessment is directed at the first three of these criteria; the last is not relevant since the product is not to be administered parenterally.

The Marketing Authorisation Application (MAA) was assessed separately and in parallel with the reclassification application. The proposed MA is identical to the reference MA, apart from some differences which relate directly to the reclassification. There are no changes to the product itself and no pharmaceutical issues to address.

PHARMACEUTICAL ASSESSMENT

1 *INTRODUCTION*

LEGAL BASIS

This is a national simple abridged application for a cream containing 1%w/w penciclovir. It was submitted under Article 10c of Directive 2001/83/EC as amended. The reference product is Vectavir Cold Sore Cream (PL 00030/0210). Novartis Consumer Health UK Limited is the marketing authorisation holder for both the reference product and the pending product.

No paediatric development plan exists for this product.

USE

The product is for the treatment of *Herpes labialis* infections (cold sores).

LEGAL STATUS

This abridged application was accompanied by a reclassification application which sought to change the legal status from POM to P. The amended assessment report for the reclassification application can be found immediately after the Pharmaceutical Assessment.

2 *DRUG SUBSTANCE*

MANUFACTURER

The manufacturer has provided a written undertaking to inform the applicant in case of modification of the manufacturing process. A statement from the competent authority which carried out the inspection of the manufacturing sites has been supplied. The manufacturer and in process controls are the same as the reference product.

3 *DRUG PRODUCT*

MANUFACTURER

Valid manufacturing licences have been provided for the manufacturers. The qualitative composition of Fenistil Cold Sore Cream is given below

Penciclovir
Liquid Paraffin
Cetostearyl Alcohol
Propylene Glycol
Water Purified
Cetomacrogol 1000
White Soft Paraffin

Manufacture of the finished product is the same as the reference product.

CONTAINER CLOSURE SYSTEM

The containers licensed for the reference product are aluminium tubes of 2G and 5G, and pump dispensers of 2G. The applicant proposes to market the reclassified product in 2G tubes only; other pack sizes and packaging types were removed from the application.

TSE

The applicant has stated that there are no materials of animal and/or human origin contained in or used in the manufacture of the medicinal product.

4 *ASSESSOR'S COMMENTS ON MODULE I*

NAME

The proposed product name, Fenistil Cold Sore Cream, is considered to be acceptable.

SPC

This will be assessed in connection with the reclassification application.

PATIENT INFORMATION LEAFLET

This will be assessed in connection with the reclassification application.

LABEL

This will be assessed in connection with the reclassification application..

5 *EXPERTS*

The applicant has provided quality, non-clinical and clinical overviews written by suitably qualified experts.

The quality overview confirms that the manufacture, control procedures and specifications for the pending product are identical to those for the reference product.

The non-clinical overview states that there are no new preclinical data to support this application.

The clinical overview is written in support of the reclassification application.

ASSESSOR'S OVERALL CONCLUSIONS

The pending MA is identical to the reference MA, apart from differences arising directly from the associated reclassification application, and the removal of some redundant company information. A marketing authorisation was granted.

RECLASSIFICATION APPLICATION

The proposed name, Fenistil Cold Sore Cream, was considered to be acceptable as was proposed pack size of 2g. This is sufficient for a single course of treatment and is appropriate. The pack size is consistent with that authorised for OTC aciclovir cold sore creams.

Product Information
A number of minor pharmaceutical points led to changes in the SPC, labelling and patient information and the new SPC, PIL and packaging are appended to the Public Assessment Report.

1 MEDICAL ASSESSMENT

This medical assessment considers the POM criteria (see Section 'Proposed changes' above). Particular attention is paid to those areas where it was considered that the POM criteria might apply; these areas relate to resistance (POM criterion 1 - indirect danger) and lack of post-marketing safety data (POM criteria 3 and 1 – direct danger). Satisfactory expert reports were provided from clinical, microbiological and dermatological experts.

First POM Criterion
The product is likely to present a danger either directly or indirectly, even when used correctly, if used without medical supervision.

Direct danger - The safety profile of penciclovir is discussed in the Safety Assessment below.

Indirect danger - With regard to the indirect dangers of penciclovir supply, the two most relevant issues are diagnosis without supervision and the potential for development of viral resistance. As regards 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.

The issue of resistance is discussed in Section 5 Viral Resistance below.

Second POM Criterion

The product is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health.

There is little evidence that the prescription product has been used incorrectly, and no evidence to suggest that the pharmacy product would be used incorrectly. Penciclovir is not considered a drug of abuse or addiction. The small pack size (2g) means that it is unlikely to be used for other conditions such as herpes zoster.

Examination of ADROIT data suggests that there have been no concerns about use in children. Nevertheless the product will be restricted to children 12 years and over and will only be supplied under supervision of a pharmacist. 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 prescription medicine. The standard label warning "keep out of reach and sight of children" will be applied.

There are no concerns about overdose, as the systemic bioavailability is low. The applicant reports 6 cases of drug abuse and 5 cases of accidental injury or medication error. These are described in the Safety Assessment below.

The dosing recommendations for penciclovir cream differ from those for aciclovir cream. For penciclovir the dose is applied every 2 hours for 4 days, for aciclovir it is every 4 hours for 5 - 10 days. Aciclovir is licensed for use in children less than 12 years of age; penciclovir is not. It is possible that patients familiar with aciclovir cream may be confused when they use penciclovir cream and use it incorrectly. However, since non-prescription supply will be through pharmacies, there will be a pharmacist available to advise the patient of the differences between the products.

The directions for use for Fenistil Cold Sore Cream recommend application every 2 hours during waking hours. Assuming a sleeping period of 8 hours, this would necessitate 8 or 9 applications a day. Since the likelihood of non-compliance increases with the dose frequency, there is a possibility that the patient may miss one or more doses. Again, the advice of the pharmacist will be of value in reinforcing the importance of compliance with the recommended dose.

The application therefore raises no concerns in relation to overdose, use in children or misuse / abuse.

Third POM Criterion
Contains substances the activity and/or side effects of which require further investigation.

The safety profile of penciclovir is now well established and is discussed in the Safety Assessment of this report.

2 COMMITTEE CONSIDERATION

The CSM considered the application in October 2005 and advised that, on the basis of the evidence before them, Fenistil Cold Sore Cream, containing 1% penciclovir, could safely be supplied without a prescription under the supervision of a pharmacist, under the following conditions:

- for external use
- maximum strength 1%
- for the treatment of herpes simplex virus infections of the lips and face (*Herpes labialis*)
- for use in patients aged 12 years or more
- in a container or package containing not more than 2g of product

3 CONSULTATION

Consultation document ARM 35, which summarises the proposals for Pharmacy supply of Fenistil Cold Sore Cream, was posted on the MHRA website on 18 January 2006. The deadline for comments was 28 February 2006.

Nineteen responses to consultation were received. None of the respondents was opposed to the proposal; 11 supported it, 4 raised no objection, and 4 made no comment.

The respondents were from a medical, pharmaceutical or nursing background. Three respondents suggested amendments to the product information,

RECOMMENDATIONS

Consultation raised no new issues, and there were no objections to the proposed reclassification; it was recommended that the application be processed to approval. During the assessment and consultation processes, several deficiencies in the product information were identified. The applicant was informed of these and the appropriate changes to product information were undertaken.

4 SAFETY ASSESSMENT

Spontaneous Reporting Systems
Between 4th June 1996 and 31st October 2004 , 480 patients reported 665 individual adverse events. All but 4 reports were classified as non-serious. The commonest reactions included *application site reaction* (62), *drug ineffective* (24), *therapeutic response decreased* (198). This includes POM and OTC penciclovir use. Of the 4 serious adverse events, three had plausible alternative causes and one had insufficient information to assess causality. There were 6 reports of drug abuse and 5 cases of accidental injury or medication error. The expert states that these involved patients who had inadvertently applied penciclovir to the eye or who had accidentally ingested the cream. There were no serious or long-term effects.

ADROIT data
Extract period Jul 63 – Sep – 05
Earliest reaction Apr 02

System Organ Class	Number of ADRs
General disorders and administration site reactions – application site reaction	1
Skin and subcutaneous tissue disorders – skin injuries and mechanical dermatoses scar	1
Total	**2**
Fatal	0

No change in the SPC was required on the basis of this data. Compared to the volume of sales the number of Adverse Drug Reactions (ADRs) is low.

Retrospective Studies of Post-Marketing Surveillance Databases
The applicant has summarised data from two UK PMS (Post Marketing Surveillance) databases, the MediPlus Database and the General Practice Research Database (GPRD). These databases examined the safety profiles of penciclovir cream and aciclovir cream, over the two years following penciclovir's launch in 1996. The most common clinical events were *respiratory infections* probably reflecting background rates since they were unrestricted by age and apparently unrelated to penciclovir cream. *Dermatological and hypersensitivity* events were non-serious and similar across groups. These results do no raise any new safety concerns with regard to the relative safety of penciclovir and aciclovir.

Clinical Trials
Six trials were discussed at length in the safety summary. The clinical expert also singles out four other studies - one of which was in genital herpes - for comment in the safety summary, none of which showed any serious or unexpected adverse events. The commonest events were *skin reactions*. No new safety concerns have therefore been raised.

Conclusions on safety
Review of post-marketing safety data to date has raised no safety concerns.

5 VIRAL RESISTANCE

The European Commission has previously expressed concern regarding the availability of antimicrobial agents without prescription[1.] Concerns about the development of viral resistance were addressed in the dossier. The Applicant submitted additional information which included two expert reports and two previously unconsidered studies to support the reclassification application. Both the microbiology expert report and the applicant's clinical overview are referred to in the following section.

5.1 Mechanisms of Antiviral Action and Resistance

Penciclovir is a synthetic acyclic guanine derivative, similar to aciclovir, which in herpes simplex (HSV) infected cells is converted by viral thymidine kinase (TK) to penciclovir monophosphate, and then by cellular kinases to the triphosphate form. In vitro studies have shown that penciclovir triphosphate inhibits HSV polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and therefore replication are selectively inhibited. Penciclovir has been shown to have antiviral activity against both HSV type 1 and HSV type 2.

Aciclovir (ACV) and penciclovir (PCV) have essentially the same mode of action, though penciclovir is a less potent inhibitor of viral DNA polymerase. This is countered by the more efficient phosphorylation by viral TK, higher intracellular concentrations and longer half-life of penciclovir.

Resistance is based on either a deficiency or an alteration in viral (thymidine kinase) TK activity, or a mutation in the DNA polymerase gene. (See **Table 1**). It is noted that there are however minor differences between the two - mutations in the TK gene do not necessarily occur at the same site, and they are not of the same type (e.g. frameshift mutations versus non conservative amino acid changes). There are also pharmacokinetic and pharmacodynamic differences.

Assessor's comment
Since there is a high degree of cross resistance between penciclovir and aciclovir, any discussion of viral resistance to penciclovir also requires consideration of resistance to aciclovir. The effect of differences between the two drugs on the potential of PCV to increase the risk of viral resistance to some extent is minimal. If PCV were to have different mechanisms of resistance to ACV, then it would be more useful to keep it as a second line drug, and therefore would argue against making more widely available. However the consensus at present is that they are similar enough and reclassification is less of a risk in this regard.

About 95% of ACV or PCV resistant isolates are TK^N or TK^p strains. These viral mutants show reduced virulence compared to wild type (normal) virus[2,] depending on the degree of TK deficiency.

Table1. Types of HSV resistance to aciclovir and resulting degree of resistance to penciclovir. Wild type virus (TK^+) has 40-100% of normal TK activity

Virus type*	Definition	Resistance to penciclovir
TK-negative (TK^N)	No TK activity	Always resistant
*TK-partial (TK^p)	1-15%of normal TK activity	Almost always resistant
*TK-altered (TK^a)	>15% or normal TK activity, but phosphorylation of aciclovir and penciclovir is impaired	Usually resistant
DNA polymerase	DNA polymerase gene mutation, producing inability to recognise aciclovir / penciclovir triphosphate	Maybe sensitive
TK plus polymerase (double mutants)	Combination of a TK deficiency and DNA polymerase mutation	Usually resistant

(* some strains cannot be classified clearly as TK^p or TK^a strains, i.e they exhibit a reduced TK activity, but phosphorylate natural substrates such as thymidine considerably more efficiently than ACV or PCV)

Although TK activity appears to be an important indicator of virulence, pathogenicity and ability to reactivate from a latent state, in some tissues cellular TK can assume the function of the viral enzyme, and therefore some TK^N or TK^p strains may show considerable pathogenicity. However, this is mainly seen in immunodeficient patients.

DNA polymerase mutants have also been shown to work in the presence of high concentrations of tri-phosphorylated ACV and PCV. Relevant mutants can also mediate a cross-resistance to other agents that act on this enzyme. E.g. foscarnet. ACV and PCV may not however show cross resistance with respect to DNA polymerase. Some ACV resistant DNA polymerases show retained or even enhanced PCV sensitivity.[3] Resistance involving DNA polymerase appears to be rare and may be associated with immunosuppression.

Double mutants in the region of TK and DNA polymerase have a broad spectrum of resistance to the majority of antiviral agents with HSV activity[4].

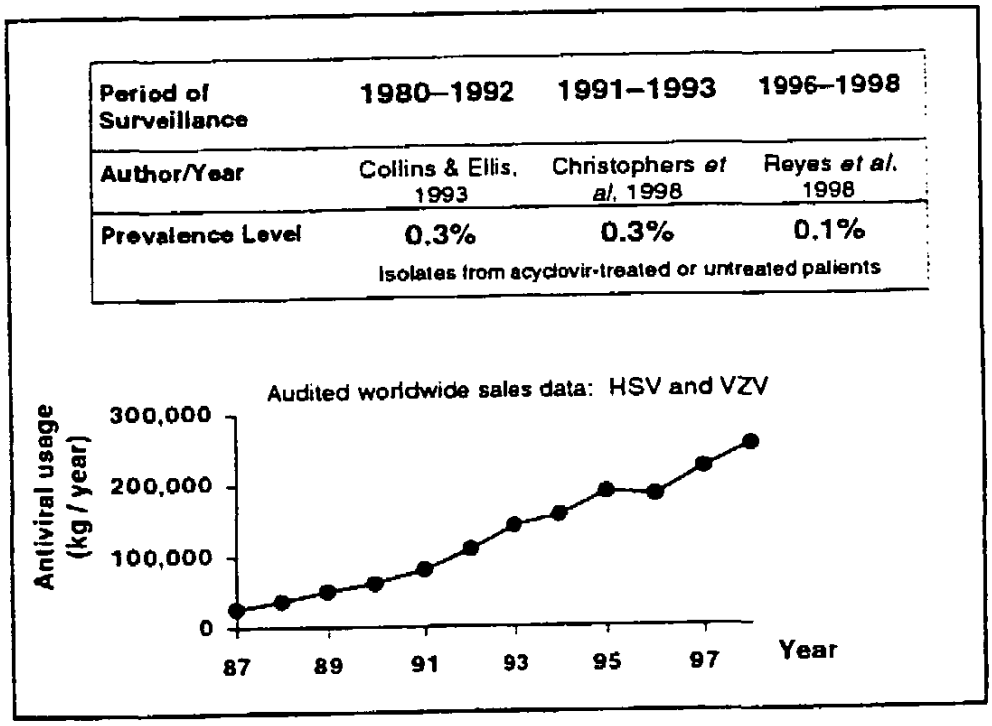
Assessor's comment
For strains that are TK deficient, cross resistance can be shown between all agents that require TK for phosphorylation i.e. ACV, PCV and ganciclovir. These strains would still be sensitive to e.g. foscarnet and cidofovir as they act on DNA polymerase (see fig.1). However DNA polymerase resistance induced by e.g. ACV would also show resistance to foscarnet, cidofovir or vidarabin.

5.2 Aciclovir Resistance Data

The applicant has provided data on several surveillance studies from the US, UK and France, and cites a prevalence of ACV resistance in immunocompetent individuals of 0.1% to 0.7%.[5] These references suggest HSV prevalence levels have remained stable over the last 20 years.

There is some evidence that even with long-term (at least 6 years) suppressive oral therapy in patients with recurrent genital herpes who started therapy in 1984 there has been no change in susceptibility.[6] Most ACV-resistant HSV isolates from immunocompetent individuals have been detected in the course of recurrent genital herpes.[7]

The Figure below gives an historical overview of surveillance data (*plaque reduction method*) and shows aciclovir resistant HSV prevalence level against the increasing total antiviral usage worldwide.



Assessor's comment
In trying to predict the effect of wider availability of PCV on HSV resistance, conclusions may be extrapolated from aciclovir data. These suggest resistance levels have remained relatively stable in the immunocompetent population despite the wider availability of aciclovir therapy. Prevalence figures from 1998 to 2003 are similar (see below)

5.3 New Studies

The applicant discussed the results of two unpublished studies :

5.3.1 The first study examined the prevalence of naturally occurring in vitro resistance to nucleoside analogues. This suggested a mutation rate for HSV-1 of 6-8 mutants per 10^4 viruses – commonly in the TK gene. The mutation rate however was much higher with HSV-

2 strains than with HSV-1 strains suggesting that HSV-1 had a lower risk of developing resistance in vivo than HSV-2.

5.3.2 The second study was a survey which examined the susceptibility of HSV to acyclovir and penciclovir among isolates from immunocompetent subjects with recurrent herpes labialis in the UK. From a total of 1304 patients who were untreated with antiviral treatment (oral or topical) at the ulcer stage, 1297 swabs were taken of which 924 (71.2%) were positive for HSV. Of these, 920 were HSV-1, 2 were HSV-2, and 2 were of mixed type. Only one isolate was scored as resistant to ACV and the same one was also resistant to PCV (prevalence of 0.11% each (1/924 and 1/915)). The IC_{50} for certain subgroups were analysed to assess whether those who had previous exposure to antivirals, were more likely to show phenotypic resistance than those without previous antiviral use. Seventy five percent of evaluable patients in this study had previous reported use of OTC topical aciclovir (approximately 2.2% had previous penciclovir experience). The applicant stated that HSV-1 isolates from subjects who had used antiviral medication previously to treat cold sores were no more susceptible to aciclovir or penciclovir resistance than HSV isolates from subjects who had never used antiviral medication ($p = 0.13$ and $p = 0.94$, respectively). They conclude that the prevalence of aciclovir resistance was low even after 5 years of non-prescription use of aciclovir in the UK.

Assessor's comments
While it is encouraging that there seemed to be no difference in antiviral susceptibility between patients who had used topical aciclovir previously and those without previous exposure, the Applicant also stated that 20 patients had used HSV specific antivirals for a condition other than a cold sore. It is not clear how these 20 were distributed between the two groups – if they were mostly in the no previous topical aciclovir group, this may have reduced any difference between the two groups. The statistical calculations were not presented in the dossier.

5.4 Studies with Penciclovir

Sarisky et al[8] examined penciclovir (and famciclovir) sensitivity in isolates from patients participating in 11 world wide clinical trials in 2003. PCV resistant HSV was isolated in 0.22% immunocompetent patients and 2.1% of immunodeficient patients. This was consistent with aciclovir clinical experience. In these studies, while treatment with topical PCV was not associated with the development of resistance, both oral and IV PCV led to the development of at least partial resistance in two immunodeficient patients.

In another UK study[9] investigating the resistance profile of serial HSV isolates over 4 days of either topical PCV treatment or placebo, 2 out of 1,025 isolates (two patients in 585) showed PCV resistance. These samples were taken within 17 hours of treatment and subsequent isolates from the same patients were sensitive. The relation between treatment and resistance remains unclear and the authors suggested various mechanisms including presence of a pre-existing variant, as well as the result of selection pressure from the antiviral treatment. However preferential selection for resistant variants, followed by selection against these isolates on grounds of reduced fitness also could not be ruled out. There were however 3 patients in the PCV group (and one in the placebo group) who had slight increases in the average PCV inhibitory concentration. No PCV resistance developed in any of these cases.

The authors make the comment that the distribution profiles of the majority of isolates overlapped, suggesting no significant differences between the two groups.

Shin et al. (2003), using a more sensitive (*plating efficiency)* assay to assess HSV resistance in 110 patients, found that those who were receiving 4 days topical treatment over consecutive episodes, showed signs of an increasing subpopulation of resistance in some isolates. This was despite viral isolates remaining sensitive to PCV throughout treatment when tested by *plaque reduction* assay. This subpopulation did not increase with subsequent recurrences however, and invariably remained a minor subpopulation. It was concluded that resistant variants did not accumulate in the sensory ganglia of immunocompetent patients.

Assessor's comment
Examination of the PCV data suggests the incidence of penciclovir resistance when topical treatment is used is low and without clinical consequence. This may be partly because it is difficult to assess whether viral resistance, even if measured by inhibitory concentration, has actually led to treatment failure. Since the disease is self limiting and of only a few days' duration, and penciclovir will on average only shorten the disease duration by about 1 day, then treatment failure may not be apparent to the patient or physician. Another explanation may be as hypothesised in Shin et al (2003), that peripheral resistance arising from topical treatment does not lead to resistance in the sensory ganglion, since latent virus present here is not subject to any selection pressure by virustatic treatment. Thus future episodes may still be responsive to the antiviral agent.

5.5 Resistance in Immunodeficient Populations

The prevalence of resistant isolates in immunodeficient patients is between 3 and 7%. In bone marrow transplant patients, though this has been as high as 30%. The immunodeficient face a greater risk of developing resistant HSV than an immunocompetent host because:

• Recurrent HSV infections in immunodeficient patients may be more severe leading to progressive disease which requires prolonged antiviral therapy
• The duration of virus replication is extended and high viral titres may persist

The applicant comments that over the last 20 years the use of both systemic and topical antivirals to treat HSV has increased dramatically, but that surveys have failed to show any increase in the prevalence of resistance in either the immunocompetent (Bacon et al (2002), Reyes et al (1998), Collins and Ellis (1993); Christophers et al (1998), Nugier et al 1992) or the immunodeficient population (Reyes et al (1998), Gnann et al (1999)) despite the HIV epidemic and widespread use of aciclovir, valaciclovir, penciclovir and famciclovir for the treatment and suppression of recurrent genital herpes. Morfin and Thouvenot (2003) found no increase over 10 years in the incidence of resistance to aciclovir in the immunodeficient population in France.

Cases of clinically significant aciclovir-resistant HSV infection appear limited almost exclusively to the immunodeficient population in which the degree of immunosuppression and the duration of therapy are influential factors in resistance development[10.] The degree of immunosuppression appears to play a role in the development of resistance by influencing host factors important in limiting viral replication.

Assessor's comment
The Clinical Expert considered the possibility that wider availability of PCV may have more impact on the immunodeficient, since resistance to antiviral agents is likely to be more of a problem in this group. However he is unable to comment on the epidemiological role of these patients in the spread of resistant strains. The expert concludes that self medication in this group should be avoided. For pharmacy supply of penciclovir cream, the SPC will state that this medication is not recommended for this group, and that such patients must be advised to attend their doctor for assessment of their lesion. This in line with the SPC of OTC aciclovir.

5.6 Spread of Resistance

The clinical expert refers to a mathematical model[11] which was devised to analyse the effect of antiviral treatment on the transmission of, and prevalence of drug resistance in, HSV -1 in the US in 2000. The authors first modelled the effects of current antiviral use and then used the model to predict the effects on transmission / resistance of a large increase in usage as might be seen with a reclassification of PCV to OTC use.

The expanded model, which allowed for acquired resistance and included immunodeficient hosts and other more realistic features, predicted that current antiviral use was unlikely to lead to any noticeable increase in resistance. If antiviral use increased, the resulting rise in resistance in the population would depend primarily *on the probability that immunocompetent hosts acquire permanent resistance upon treatment*. This probability was known to be small, but its exact value remained uncertain. The authors calculated 95% confidence intervals for this probability (0, 0.0016). These figures came from an analysis of 1,900 patients studied for emergence of resistance during nucleoside analogue treatment – out of which 0 had resistance on plaque reduction assay. The results showed that if acquired resistance occurred less than once per 2,400 treated episodes (an intermediate prediction), then in the community at large, the frequency of HSV-1 resistance was predicted to increase slowly, remaining below 0.5% for > 50 years, even with extensive nucleoside analogue use. If acquired resistance emerged in 1 per 625 treated episodes (the maximum of an approximate 95% confidence interval derived from the results of several studies of resistance in treated hosts), then the prevalence of infection with resistant HSV-1 could rise from about 0.2% to 1.5 to 3% within 50 years. Thus the authors used values in their model that would produce the slowest and fastest increases in the prevalence of resistant infection.

Assessor's comment
There are some limitations to this study (which was funded by the MA Holder at the time):
- The sample size is small given the rarity of the event.
- The projections are based on the IC_{50} results of plaque reduction assay to diagnose resistance. If a resistant strain was only a small proportion of the total virus population, then it is unlikely to be detected by the assay. This could substantially underestimate the true probability of acquired resistance, particularly if it occurs by means of successive 'enrichments' of the resistance population during successive treated episodes.
The author however makes the point that these results are consistent with the observation that HSV-1 prevalence has remained relatively flat despite nearly 20 years analogue use. This fact is more reassuring than the mathematical model described.

5.7 Resistance: Conclusions

The prevalence of resistant HSV-1 has remained low and stable over nearly 20 years despite widespread and increasing use. The applicant has suggested a number of plausible virus and host factors which reduce the likelihood of resistance development. These include slow viral dynamics, reduced virulence of resistant virus, and a relatively weak selection pressure from the topical antiviral (high local concentrations for a short period). Host factors include the theory that viral resistance in a peripheral lesion does not seem to lead to the establishment of resistance centrally in the sensory ganglion.[12] Also, hypothesised is that viral clearance by the host immune system in a coldsore is quick – typically less than 10 days – reducing the length of time virus and antiviral are in contact.

The authors of the mathematical model suggest the rate of spread of resistance should be addressed through long term monitoring of virus isolates from individuals who repeatedly treat occurrences with antiviral drugs. They conclude that the methodology of such studies should include the measurement of subpopulations of resistant viruses within the heterogeneous sample. This would enable the assessment of gradual increases in the proportion of resistant viruses during successive rounds of treatment.

Assessor's comment

The resistant subpopulations associated with topical penciclovir use in the immunocompetent population are rare, have had no clinical impact to date and therefore remain a theoretical risk. The experience with aciclovir has been that a significantly increased prevalence of resistance has not taken place with widespread use. The applicant refers to various studies from 2002 and 2003 where the prevalence of aciclovir and penciclovir resistance was stable at 0.1-0.7% despite POM and OTC use of both. Though the applicant's expert echoes the authors of the mathematical model regarding the importance of monitoring resistance development, particularly in those individuals who treat coldsore occurrences repeatedly, no such monitoring was required for pharmacy supply of aciclovir (which switched to OTC in 1993). This product was also reclassified from P to GSL supply in 2004 without any commitments to monitor resistance prevalence.

There would be practical difficulties in setting up a formal monitoring of the effects on viral resistance following the use of an OTC product and therefore it may be more appropriate to review the prevalence of resistance at an agreed time point following deregulation. A UK survey has already been carried out on topical antivirals and it is possible this may be the most efficient method of assessing this concern

It is clear that the immunodeficient remain the most likely group to develop resistance virus. The clinical expert states that it is difficult to predict the epidemiological role of these patients in transmitting resistant virus. Despite an apparent lack in increased prevalence, one study on treatment of genital herpes in the immunodeficient showed no increase, despite the widespread use of oral and topical aciclovir, valaciclovir, penciclovir and famciclovir. The SPC was changed to state that penciclovir is not recommended for use in the immunocompromised and not as previously "severely immunocompromised". For pharmacy supply of this drug, the word 'severely' will be removed from 4.4 in order to clarify that OTC supply of penciclovir is not recommended for all immunodeficient patients, and that this group should be advised to see their doctor. Together with the inclusion of a new statement about immunocompromised patients in section 4.1, these sections are brought in line with the current approved OTC aciclovir cold sore cream SPC.

6 Product Information

6.1 Summary of Product Characteristics (SPC)

A number of changes to the SPC were made to clarify the location of cold sores to be treated by this product, to emphasise that Fenistil is for use in the over 12's and that immunocompromised patients should seek medical advice. The revised SPC can be found on page 20 of this Public Assessment Report.

6.2 Labelling and Patient Information Leaflet (PIL)

Changes to the labelling and PIL were made to reflect changes to the SPC and to improve readability, the labels and PIL can be found from page 26 of this report.

7 Pharmacist Training

Pharmacists are accustomed to counter prescribing for cold sores, and have had over 10 years experience with a non-prescription antiviral treatment, namely aciclovir. The assessors agree with the applicant's view, that pharmacists and their staff do not require any specialised training in order to supply penciclovir safely and effectively

8 Discussion

The concerns with regard to this POM to P reclassification of penciclovir cold sore cream have been the establishment of its safety profile, and the prevalence of resistant HSV. Review of the safety data leads to the conclusion that no safety concerns have been identified. The safety profile of penciclovir cream is essentially similar to that of aciclovir cold sore cream which is already available without prescription.

The evidence presented suggests that the current prevalence of resistance to aciclovir has remained stable in both immunocompetent and immunodeficient populations over the last 20 years, in the face of a marked increase in use. Several studies looking at topical penciclovir use in the UK and internationally have shown a low level of resistant virus similar to aciclovir. Where resistance is detected with more sensitive assays, increases in IC_{50} in subpopulations have been detected, but without apparent clinical consequence. Mathematical modelling based on resistance determined by the plaque reduction assay, suggests only a slow increase in resistance rates over the next 50 years (<5%). It is not yet clear whether the resistant viral subpopulations, only identified with more sensitive assays, accumulate with time or whether they will eventually contribute to the spread of resistance. It is of note that these subpopulations are very rare, and have been found in placebo treated populations as well those who used penciclovir. Experience with aciclovir so far suggests a significant increase in resistance has not happened despite widespread use.

The benefits of monitoring for resistant viral subpopulations in those who use topical antivirals for successive coldsore episodes, as described earlier, perhaps as part of a reclassification commitment are unclear at present. It is noted that the data has suggested little increase in aciclovir resistance despite widespread use, and that aciclovir was deregulated in 1993 to P supply (and in 2004 to GSL supply), without such a commitment to

resistance monitoring. The prevalence of viral resistance should however be formally reviewed at an agreed time point, and perhaps by means of UK survey as described earlier.

In summary, the evidence submitted as part of the reclassification application supported the change of legal status and this was the view of the Committee on Safety of Medicines. A Marketing Authorisation was granted.

References

1 EC Document 501PC0333
2 Coen (1994)
3 Chiou et al (1995)
4 Crumpacker (2001)
5 Bacon et al (2002)
6 Fife et al (1994)
7 Morfin and Thouvenot (2003); Fife et al (2004)
8 Sarisky et al, Archives of Virology, 2003
9 Sarisky et al, Agents and Chem (2002)
10 Englund et al (1990)
11 Lipsitch et al (2002)
12 Coen et al (1996)

Overall Conclusion and Risk/Benefit Analysis

Quality
There were no new concerns regarding quality of Fenistil Cold Sore Cream.

Pre-Clinical

No new pre-clinical data were presented or were required for this type of application.

Clinical
A review of clinical safety data found that concerns over the Pharmacy availability of Fenistil Cold Sore Cream were not justified. In addition, concerns over an increase in viral resistance to increased use of Fenistil Cold Sore Cream were not found to be justified.

Risk/Benefit Analysis
It was found that the benefits of Pharmacy availability of Fenistil Cold Sore Cream outweighed the risks and a Marketing Authorisation was granted.

Steps Taken During Assessment

1	The MHRA received the application on 21st June 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 16th August 2005
3	The application was considered by the Committee on the Safety of Medicines on 27th October 2005
4	The consultation (ARM 35) was carried out between 18th January 2006 and 28th February 2006.
5	The results of the consultation, and company responses were assessed and the applications were determined on 24th August 2006.

Steps Taken After Assessment

1. Two minor (Type 1A) variations were determined on 19th October 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fenistil Cold Sore Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of the cream contains:
Active substance: 10 mg penciclovir
Excipients: cetostearyl alcohol, propylene glycol
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream
Smooth white cream of homogeneous appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fenistil Cold Sore Cream is indicated for the treatment of herpes simplex virus infections of the lips and face (herpes labialis) in adults and children over 12 years of age.
Immunocompromised patients: Fenistil Cold Sore Cream is not recommended for use in immunocompromised patients; such patients should consult a physician concerning the treatment of any infection.

4.2 Posology and method of administration

Adults (including the elderly) and children over 12 years of age:
Fenistil Cold Sore Cream should be applied at approximately two hourly intervals during waking hours, (approximately 8 times a day). Treatment should be continued for 4 days. If the condition gets worse or does not improve after 4 days treatment, seek medical advice.

Treatment should be started as early as possible after the first sign of an infection.

Children (under 12 years):
No work has been carried out in children below 12 years of age.

4.3 Contraindications

Known hypersensitivity to penciclovir, famciclovir or the other constituents of the formulation, eg. propylene glycol.

4.4 Special warnings and precautions for use

The cream should only be used on cold sores on the lips and around the mouth. It is not recommended for application to the mucous membranes, such as in the mouth or eye, or on the genitals. It must not be used in ocular or genital herpes.. Particular care should be taken to avoid contact with the eyes. Patients with particularly severe cold sores should be encouraged to seek medical advice.

Patients should be advised to avoid transmitting the virus, particularly when active lesions are present.

Immunocompromised patients (eg AIDs patients or bone marrow transplant recipients) should be encouraged to consult a physician in case oral therapy is indicated.

The cream contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis). It also contains propylene glycol, which may cause skin irritation.

4.5. Interactions with other medicinal products and other forms of interaction

Clinical trial experience has not identified any interactions resulting from concomitant administration of topical or systemic drugs with Fenistil Cold Sore Cream.

4.6. Pregnancy and lactation

There is unlikely to be any cause for concern regarding adverse effects when the cream is used in pregnant and/or lactating women as systemic absorption of penciclovir following topical administration of Fenistil Cold Sore Cream has been shown to be minimal (see Section 5.2).

Animal studies have not shown any embryotoxic or teratogenic effects with penciclovir given intravenously (at doses greater than 1200 times those recommended for clinical use via topical application), nor were there any effects on male and female fertility and general reproductive performance (at doses greater than 1600 times those recommended for clinical use via topical application). Studies in rats show that penciclovir is excreted in the breast milk of lactating females given oral famciclovir (famciclovir; the oral form of penciclovir, is converted in vivo to penciclovir). There is no information on excretion of penciclovir in human milk.

Since the safety of penciclovir in human pregnancy has not been established, Fenistil Cold Sore Cream should only be used during pregnancy or in nursing mothers on the advice of a doctor, if the potential benefits are considered to outweigh the potential risks associated with treatment.

4.7. Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Fenistil Cold Sore Cream has been well-tolerated in human studies. Clinical trial experience has shown that there was no difference between Fenistil Cold Sore Cream and placebo in the rate or type of adverse reactions reported. In particular, application site reactions (eg transient burning, stinging, numbness) occurred in less than 3% of patients in each group in the pivotal clinical trials. Post-marketing surveillance from penciclovir cream has revealed isolated cases of hypersensistivity reactions, such as allergic dermatitis, rash, urticaria, pruritis and oedema.
No cases of photosensitivity were reported in the pivotal clinical trials.

4.9. Overdose

No untoward effects would be expected even if the entire contents of a container of Fenistil Cold Sore Cream were ingested orally; penciclovir is poorly absorbed following oral administration. However, some irritation in the mouth could occur. No specific treatment is necessary if accidental oral ingestion occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Penciclovir has demonstrable in vivo and in vitro activity against herpes simplex viruses (types 1 and 2) and varicella zoster virus. In virus-infected cells penciclovir is rapidly and efficiently converted into a triphosphate (mediated via virus-induced thymidine kinase). Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits replication of viral DNA and has a half-life of 9, 10 and 20 hours in cells infected with varicella zoster virus, herpes simplex virus type 1 and herpes simplex virus type 2 respectively. 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.

In clinical studies, Fenistil treated patients healed 30% faster than placebo (up to one day earlier), pain resolution was 25-30% faster (median improvement of up to one day) and infectivity resolved up to 40% faster (one day earlier) than placebo.

5.2. Pharmacokinetic properties

Following application of Fenistil Cold Sore Cream in a human volunteer study at a daily dose of 180mg penciclovir (approximately 67 times the proposed daily clinical dose), to occluded and abraded skin for 4 days, penciclovir was not quantifiable in plasma and urine.

5.3. Preclinical safety data

General toxicology
Topical application of 5% Fenistil Cold Sore Cream for 4 weeks to rats and rabbits was well tolerated. There was no evidence of contact sensitisation in guinea pigs.

A full programme of studies has been completed using intravenous penciclovir. These studies did not raise any safety concerns regarding topical use of Fenistil Cold Sore Cream. There is a minimal systemic absorption of penciclovir following topical administration.

The results of a wide range of mutagenicity studies in vitro and in vivo indicates that penciclovir does not pose a genotoxic risk to man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

White soft paraffin
Liquid paraffin
Cetostearyl alcohol
Propylene glycol
Cetomacrogol 1000
Purified water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2g aluminium tubes - 3 years.

6.4. Special precautions for storage

Store at temperatures not exceeding 30°C.

Do not freeze.

6.5. Nature and contents of container

2g aluminium tube.

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Consumer Health (UK) Limited
Wimblehurst Road
Horsham
West Sussex RH12 5AB
UK

Trading as: Novartis Consumer Health

8. MARKETING AUTHORISATION NUMBER

PL 00030/0215

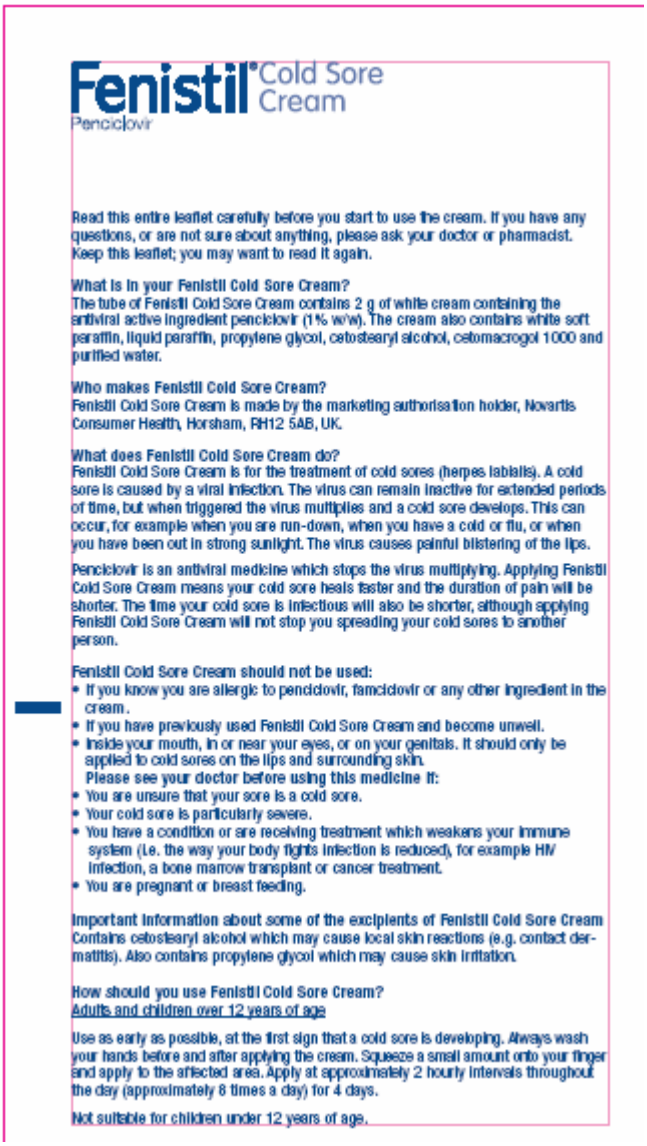
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/08/2006

10 DATE OF REVISION OF THE TEXT

23/08/2006

Labels and Leaflet



Fenistil® Cold Sore Cream
Penciclovir

Read this entire leaflet carefully before you start to use the cream. If you have any questions, or are not sure about anything, please ask your doctor or pharmacist. Keep this leaflet; you may want to read it again.

What is in your Fenistil Cold Sore Cream?
The tube of Fenistil Cold Sore Cream contains 2 g of white cream containing the antiviral active ingredient penciclovir (1% w/w). The cream also contains white soft paraffin, liquid paraffin, propylene glycol, cetostearyl alcohol, cetomacrogol 1000 and purified water.

Who makes Fenistil Cold Sore Cream?
Fenistil Cold Sore Cream is made by the marketing authorisation holder, Novartis Consumer Health, Horsham, RH12 5AB, UK.

What does Fenistil Cold Sore Cream do?
Fenistil Cold Sore Cream is for the treatment of cold sores (herpes labialis). A cold sore is caused by a viral infection. The virus can remain inactive for extended periods of time, but when triggered the virus multiplies and a cold sore develops. This can occur, for example when you are run-down, when you have a cold or flu, or when you have been out in strong sunlight. The virus causes painful blistering of the lips.

Penciclovir is an antiviral medicine which stops the virus multiplying. Applying Fenistil Cold Sore Cream means your cold sore heals faster and the duration of pain will be shorter. The time your cold sore is infectious will also be shorter, although applying Fenistil Cold Sore Cream will not stop you spreading your cold sores to another person.

Fenistil Cold Sore Cream should not be used:
- If you know you are allergic to penciclovir, famciclovir or any other ingredient in the cream.
- If you have previously used Fenistil Cold Sore Cream and become unwell.
- Inside your mouth, in or near your eyes, or on your genitals. It should only be applied to cold sores on the lips and surrounding skin.

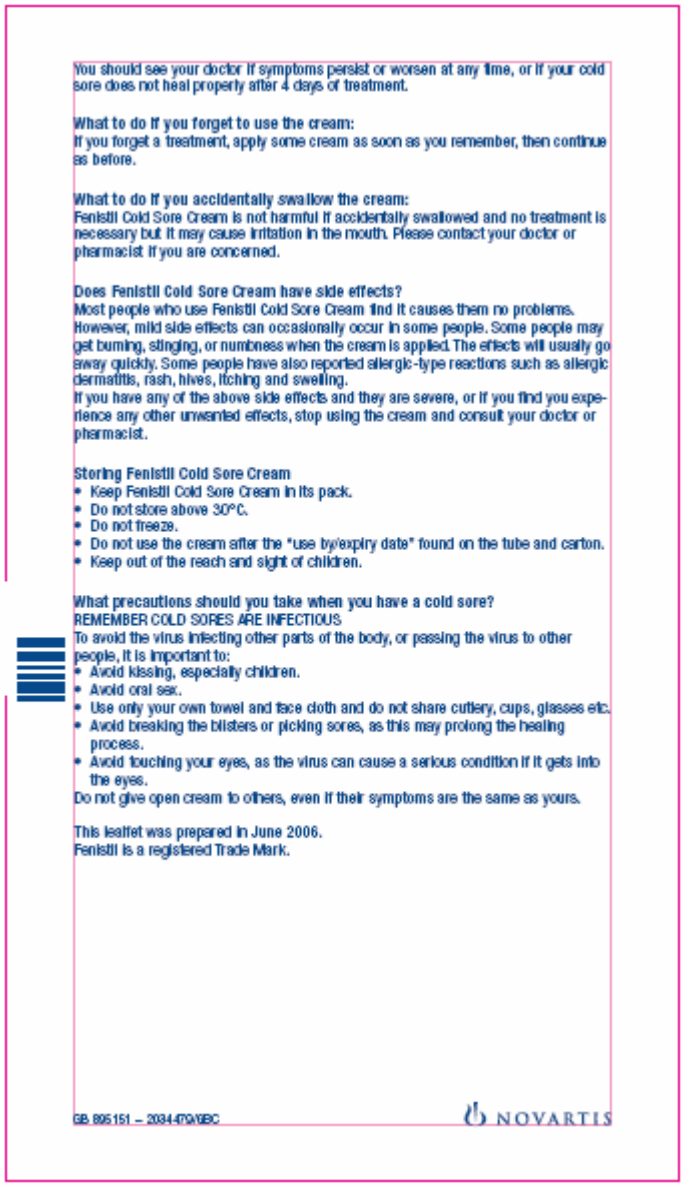
Please see your doctor before using this medicine if:
- You are unsure that your sore is a cold sore.
- Your cold sore is particularly severe.
- You have a condition or are receiving treatment which weakens your immune system (i.e. the way your body fights infection is reduced), for example HIV infection, a bone marrow transplant or cancer treatment.
- You are pregnant or breast feeding.

Important information about some of the excipients of Fenistil Cold Sore Cream
Contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis). Also contains propylene glycol which may cause skin irritation.

How should you use Fenistil Cold Sore Cream?
Adults and children over 12 years of age

Use as early as possible, at the first sign that a cold sore is developing. Always wash your hands before and after applying the cream. Squeeze a small amount onto your finger and apply to the affected area. Apply at approximately 2 hourly intervals throughout the day (approximately 8 times a day) for 4 days.

Not suitable for children under 12 years of age.



You should see your doctor if symptoms persist or worsen at any time, or if your cold sore does not heal properly after 4 days of treatment.

What to do if you forget to use the cream:
If you forget a treatment, apply some cream as soon as you remember, then continue as before.

What to do if you accidentally swallow the cream:
Fenistil Cold Sore Cream is not harmful if accidentally swallowed and no treatment is necessary but it may cause irritation in the mouth. Please contact your doctor or pharmacist if you are concerned.

Does Fenistil Cold Sore Cream have side effects?
Most people who use Fenistil Cold Sore Cream find it causes them no problems. However, mild side effects can occasionally occur in some people. Some people may get burning, stinging, or numbness when the cream is applied. The effects will usually go away quickly. Some people have also reported allergic-type reactions such as allergic dermatitis, rash, hives, itching and swelling.
If you have any of the above side effects and they are severe, or if you find you experience any other unwanted effects, stop using the cream and consult your doctor or pharmacist.

Storing Fenistil Cold Sore Cream
- Keep Fenistil Cold Sore Cream in its pack.
- Do not store above 30°C.
- Do not freeze.
- Do not use the cream after the "use by/expiry date" found on the tube and carton.
- Keep out of the reach and sight of children.

What precautions should you take when you have a cold sore?
REMEMBER COLD SORES ARE INFECTIOUS
To avoid the virus infecting other parts of the body, or passing the virus to other people, it is important to:
- Avoid kissing, especially children.
- Avoid oral sex.
- Use only your own towel and face cloth and do not share cutlery, cups, glasses etc.
- Avoid breaking the blisters or picking sores, as this may prolong the healing process.
- Avoid touching your eyes, as the virus can cause a serious condition if it gets into the eyes.

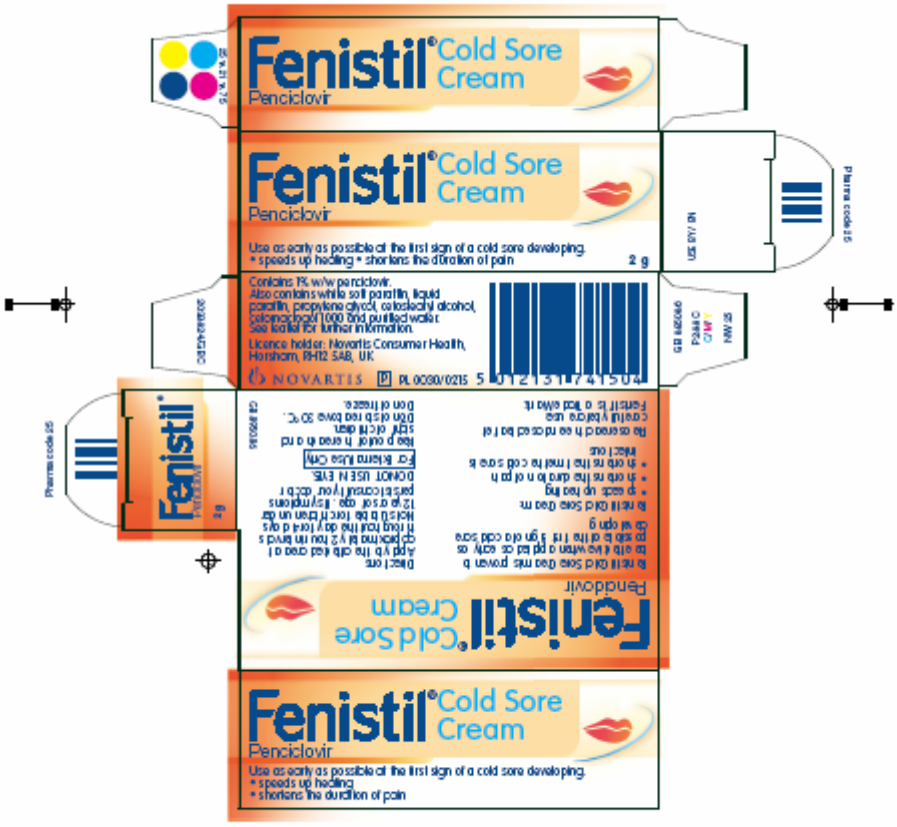
Do not give open cream to others, even if their symptoms are the same as yours.

This leaflet was prepared in June 2006.
Fenistil is a registered Trade Mark.

GB 895151 – 2034-07/06BC

NOVARTIS


Fenistil® Cold Sore Cream
Penciclovir
2 g
Apply to affected area every 2 hours throughout the day.
For External Use Only
DO NOT USE IN EYES
PL 0030/0215
NOVARTIS


Fenistil® Cold Sore Cream
Penciclovir
Use as early as possible at the first sign of a cold sore developing.
• speeds up healing • shortens the duration of pain
2 g
Contains 1% w/w penciclovir.
Also contains white soft paraffin, liquid paraffin, propylene glycol, cetostearyl alcohol, cetomacrogol 1000 and purified water.
See leaflet for further information.
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