Public Assessment Report

Decentralised Procedure

Famciclovir 500 mg film-coated tablets

(UK/H/4775/001/DC)

PL 00030/0448

Novartis Consumer Health UK Limited
**Famciclovir 500 mg film-coated tablets**

**Lay Summary**

Famciclovir 500 mg film-coated tablets
(Famciclovir)

This is a summary of the Public Assessment Report (PAR) for Famciclovir 500 mg film-coated tablets (PL 00030/0448). This summary explains how Famciclovir tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Famciclovir tablets.

For practical information about using Famciclovir tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Famciclovir tablets and what are they used for?**

Famciclovir tablets are an antiviral medicine which stops the infecting virus from reproducing. It is used to treat cold sores (herpes labialis) of the lips in adults. Cold sores are an infection caused by a virus called herpes simplex type 1.

**How are Famciclovir tablets used?**

As viruses reproduce at a very early stage in the infection, it is better for patients to take Famciclovir tablets as soon as symptoms appear. The daily dose and length of treatment depends on the type of viral infection and whether the patient’s immune system is working normally; details of the correct dose to be taken are included in the package leaflet.

**How do Famciclovir tablets work?**

When it is inside the body famciclovir is converted into another antiviral medicine called penciclovir. Penciclovir blocks the action of a viral enzyme called DNA polymerase inside infected cells. The viruses need the DNA polymerase enzyme to multiply and survive so, by blocking this, penciclovir stops the virus from spreading.

**How have Famciclovir tablets been studied?**

Famciclovir tablets are identical to another product that has already been approved to treat shingles and genital herpes. However, to demonstrate that Famciclovir tablets can also be used to treat cold sores a study was carried out in adults to investigate whether the time taken for cold sores to heal decreased when patients took Famciclovir tablets.

**What benefit have Famciclovir tablets shown during studies?**

It was shown that, in adults with an immune system that is working normally, Famciclovir tablets shorten the time taken for cold sores to heal. The effects of treatment with two doses of 750 mg famciclovir (taken on the same day) and a single dose of 1500 mg famciclovir were compared. Treatment with one 1500mg dose was found to be slightly more effective.

**What is the risk associated with Famciclovir tablets?**

The main side effect that was reported was headache; this side effect is very common and affects more than 1 in 10 people. Other side effects are dizziness, nausea and vomiting, abnormal liver function tests, rash and pruritus; these side effects affect less than one in 10 people but more than one in 100 people. For a full list of all side effects reported with Famciclovir tablets, please see the package leaflet.

Famciclovir tablets should not be used in people who are hypersensitive (allergic) to famciclovir or any of the other tablet ingredients, or to penciclovir.
Why are Famciclovir tablets approved?
It was concluded that, Famciclovir tablets are effective in treating cold sores. It was considered that the benefits of using Famciclovir tablets outweigh the risks and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Famciclovir tablets?
A risk management plan has been developed to ensure that Famciclovir tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Famciclovir tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Famciclovir tablets
Austria, Germany, Denmark, Finland, Iceland, Norway, Sweden and the UK agreed to grant a Marketing Authorisation for Famciclovir tablets on 31 October 2013.

The Marketing Authorisation for Famciclovir tablets was granted in the UK to Novartis Consumer Health UK Limited on 8 April 2014.

The full PAR for Famciclovir tablets follows this summary.

For more information about treatment with Famciclovir tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2015.
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I  Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Famciclovir 500 mg film-coated tablets could be approved. This prescription only medicine (POM) is used for the following:

- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults
- the treatment of herpes zoster in immunocompromised adults
- the treatment of first and recurrent episodes of genital herpes in immunocompetent adults
- the treatment of recurrent episodes of genital herpes in immunocompromised adults
- the suppression of recurrent genital herpes in immunocompetent and immunocompromised adults
- the treatment of recurrent episodes of herpes labialis in immunocompetent adults.

This Decentralised application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Famvir 500 mg tablets (PL 00101/0623) licensed to Novartis Pharmaceuticals UK Ltd. The reference product was initially authorised to SmithKline Beecham plc (under Marketing Authorisation number PL 10592/0112) on 17 February 1998 but, following a change of ownership on 29 August 2001, the Marketing Authorisation is owned by Novartis Pharmaceuticals UK Ltd. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

Famciclovir is the oral prodrug of penciclovir. Famciclovir is rapidly converted in vivo into penciclovir, which has in vitro activity against herpes simplex viruses (HSV types 1 and 2), varicella zoster virus, Epstein-Barr virus and cytomegalovirus.

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to in vivo conversion to penciclovir. In virus-infected cells the viral thymidine kinase (TK) phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. This triphosphate persists in infected cells in excess of 12 hours and inhibits viral DNA chain elongation by competitive inhibition with deoxyguanosine triphosphate for incorporation into the growing viral DNA, thus halting replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Hence, the probability of toxicity to mammalian host cells is low and uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

Famciclovir 500 mg film-coated tablets are bioequivalent to the reference product Famvir 500 mg tablets (PL 00101/0623). The indications for these products are the same, apart from the additional indication for Famciclovir 500 mg film-coated tablets to treat recurrent episodes of herpes labialis in immunocompetent adults. Therefore, the development programme for this application consisted of a pivotal clinical study for the one-day treatment of recurrent herpes labialis. Additional studies in recurrent herpes labialis and recurrent genital herpes were provided as supportive information. These studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent
authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at Day 210 of the procedure on 31 October 2013. After a subsequent National phase, a Marketing Authorisation was granted in the UK on 8 April 2014.
II Quality aspects

II.1 Introduction
Famciclovir 500 mg film-coated tablets are white, oval, biconvex film-coated tablets debossed with ‘FV’ on one side and ‘500’ on the reverse side.

Each film-coated tablet contains 500 mg famciclovir, lactose anhydrous, hydroxypropylcellulose, sodium starch glycollate (type A) and magnesium stearate, which make up the tablet core, and hypromellose, titanium dioxide (E171), macrogol 4000 and macrogol 6000, which make up the tablet coat.

The tablets are supplied in PVC/PVdC/aluminium blister packs. Pack sizes of 3, 14, 21, 30, 50 or 56 film-coated tablets have been authorised, although not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations concerning use of materials in contact with food.

II.2 Drug Substance

Famciclovir

INN: Famciclovir
Chemical Name: 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl acetate

Structure:

Molecular formula: \( C_{14}H_{19}N_5O_4 \)
Molecular weight: 321.33
Appearance: White to pale yellow crystalline solid.
Solubility: Very soluble in methanol, sparingly soluble in ethanol and propan-1-ol and freely soluble in acetone.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An acceptable specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Acceptable stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development was to obtain a formulation with similar in vitro dissolution profiles and in vivo pharmacokinetic performance to the reference product.

Comparative in-vitro dissolution profiles have been provided for batches of the test and reference products. The dissolution profiles were satisfactory.

Appropriate justifications for the inclusion of each excipient have been provided. All excipients comply with their European Pharmacopoeia monographs with the exception of the tablet coat, however, as the tablet coat is composed of European Pharmacopoeia components, this is acceptable.

With the exception of lactose anhydrous, none of the excipients contain materials of animal or human origin. The supplier of lactose anhydrous has confirmed that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that intended for human consumption.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the medicinal product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed on batches of medicinal product in the packaging proposed for marketing and in accordance with current guidelines. The stability data support a shelf-life of 3 years when the storage precaution ‘Do not store above 25°C’ is applied.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

The MAA form is satisfactory from a pharmaceutical perspective.

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The grant of a Marketing Authorisation is recommended.
III  Non-clinical aspects

As the pharmacological, pharmacokinetic and toxicological properties of famciclovir are well known, no non-clinical studies are required and none have been provided.

Non-clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Environmental Risk Assessment
The applicant has conducted an environmental risk assessment (ERA) and the data provided suggest that the proposed use of famciclovir should not pose a risk to the environment.

Product Literature
The product literature is acceptable from a non-clinical point of view.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV  Clinical aspects

IV.1  Introduction
This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. In support of this application, one pharmacokinetic study, one pivotal Phase III study and one supportive Phase IV observational study were submitted.

All studies were conducted in-line with Good Clinical Practice (GCP).

IV.2  Pharmacokinetics

Biowaiver
A pivotal study was conducted with 250 mg capsules produced by encapsulating two 125 mg coated tablets. Famciclovir 500 mg film-coated tablets are considered to be bioequivalent to four of the 125 mg tablets since:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the compositions of the tablets are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for both strengths
d) appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing.

Data were provided to demonstrate that encapsulation of commercial 125 mg tablets does not affect the rate and extent of dissolution of famciclovir and, consequently, the bioavailability of the drug. The pharmacokinetics of famciclovir were also shown to be linear over the dose range of 125 mg–750 mg.

In line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), bioequivalence between the product used in the pivotal clinical trial and Famciclovir 500 mg film-coated tablets can, therefore, be accepted.
**Pharmacokinetic study**

This was a multicentre, open-label, single-arm safety and pharmacokinetic (PK) study using a single 1500 mg dose of famciclovir. Plasma concentration-time data were used to calculate the following pharmacokinetic parameters of penciclovir: $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $T_{1/2}$ and $\text{Cl/F}$.

A total of 53 patients were enrolled. Pharmacokinetic samples were assessed from eight patients: two in the 12 to <14 years age group, four in the 14 to <16 years age group and two in the 16 to <18 years age group.

Mean profiles of both penciclovir and its precursor 6-deoxypenciclovir are shown. Concentrations of 6-deoxypenciclovir were lower than those of penciclovir and were only measurable up to 3 to 4 hours after dosing.

**Table 1 Key PK parameters for penciclovir and 6-deoxypenciclovir in adolescents**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>$T_{\text{max}}$ [h]</th>
<th>$C_{\text{max}}$ [µg/mL]</th>
<th>$AUC_{0-\infty}$ [(µg/mL)h]</th>
<th>$T_{1/2}$ [h]</th>
<th>CL/F [L/h]</th>
<th>CL/F[BW] [L/h/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penciclovir</td>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Mean¹</td>
<td>1</td>
<td>9.37</td>
<td>31.78</td>
<td>1.81</td>
<td>38.2</td>
<td>0.60</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>2.36</td>
<td>5.53</td>
<td>0.22</td>
<td>6.1</td>
<td>0.14</td>
</tr>
<tr>
<td>6-Deoxypenciclovir</td>
<td>N</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean¹</td>
<td>1</td>
<td>3.32</td>
<td>6.61</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>2.36</td>
<td>3.89</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: ¹ = median for $T_{\text{max}}$

The clearance of penciclovir observed in adolescents (38.2 L/h) was similar to and within the range of values previously measured in adolescents.

The applicant investigated the PK of a single dose of 1500 mg famciclovir in adolescents. Based on the underlying assumption that PK are broadly similar in adults and adolescents > 40 kg, conclusions were drawn for the adult population. In view of what is known about the PK of famciclovir, the assumption seems justifiable. The $C_{\text{max}}$ and $AUC_{0-\infty}$ values observed for penciclovir in adolescents were within the range of values extrapolated from adults in another study.

In the PK study, adolescents weighing > 40 kg (mean weight 65 kg, range 53-92 kg) were given 1500 mg as a single dose resulting in a mean $C_{\text{max}}$ of 9.37 mcg/ml for penciclovir. Mean peak plasma concentration of penciclovir in adults following a 750 mg oral dose of famciclovir was 5.1 mcg/ml, providing some evidence that $C_{\text{max}}$ after 1500 mg may be proportional to $C_{\text{max}}$ after a 750 mg dose. The limited available data indicate that plasma concentration profiles in adolescents (after 1500 mg) and adults (after 500 mg, extrapolated to 1500 mg) may also be broadly similar. Exposure data in adolescents receiving 1500 mg are broadly within the range of what would be expected to be seen in adults after the same dose when extrapolating from doses of 500 mg and 1000 mg. This provides some indication that exposure to penciclovir may increase in proportion to dose up to a single dose of 1500 mg, both in adults and adolescents.

**IV.3 Pharmacodynamics**

No new data were provided and none were required for this application.

**IV.4 Clinical efficacy**

The MAH conducted one pivotal study and one supportive (uncontrolled observational) study.
Phase III pivotal study
This was a randomised, multicenter, double-blinded controlled study to compare the effectiveness two one-day regimens of famciclovir (two 750 mg doses 12 hours apart or one 1500 mg dose) compared to placebo in patient-initiated episodic treatment of recurrent herpes labialis.

Dose selection rationale
No dose finding studies have been conducted; the dose is largely based on theoretical considerations.

A high initial dose at the time of intense viral replication is in theory appropriate, although it is not clear at which level and for how long high intracellular concentrations are required for best effect.

Exploration of a short treatment period is plausible as the effect of further treatment after the appearance of skin lesions (usually in < 24h) may add little benefit in this brief, self-limiting condition. The chosen dose regimens seem acceptable for evaluation in clinical studies. The applicant clarified that the PK/ PD relationship is not known and cannot support dose finding. Demonstration of clinical efficacy in the clinical study with the chosen dose regimen suggests that the dose was sufficiently high to produce a beneficial effect, however the available information can not address the question if a lower dose may have been sufficient or if higher doses may have provided improved efficacy.

Inclusion criteria:
• Patients aged 18 years or older with a history typical for recurrent herpes labialis (three or more episodes of cold sores in the last 12 months, and have a history of prodromal symptoms, as defined by the patient, preceding at least 50% of these cold sores, and must also have a history of vesicular lesions in at least 50% of the recurrent episodes of cold sores).
• General good health, without other serious medical conditions and, specifically, with normal renal and hepatic function, as determined by the patient's account of his/her medical history
• Women of child bearing potential had to use an accepted method of birth control and a negative pregnancy test (urine) at screening was required

Exclusion criteria:
• Previous herpes vaccination
• Patients using topical immunosuppressive agents on or near the face or systemic immunosuppressive agents within 30 days of screening; patients known to be immunosuppressed (e.g. HIV infection or concomitant treatment, e.g. cancer chemotherapy)
• Recent history of alcohol or drug abuse, which in the opinion of the investigator, could interfere with that study patient’s compliance with study requirements
• Significant skin disease that would interfere with the assessment of lesions

Primary endpoint:
Investigator-assessed time to healing of the primary lesion complex (the first study lesions that appear within the first 24 hours), defined as the time from start of treatment until loss of crust (erythema may be present) for patients who progressed to vesicular/ulcer stage lesions.

Secondary endpoints:
Time to healing (loss of crust) of the primary lesion complex of all vesicular and aborted (non-vesicular) lesions based on investigator assessment, time to healing (loss of crust) of all
lesions (primary and secondary vesicular lesions and aborted lesions) based on investigator assessment, time to return to normal skin for all lesions, the percentage of patients with aborted (non-vesicular) lesions, the percentage of patients with lesion tenderness or pain and the duration of lesion tenderness or pain, defined from the onset to the time of disappearance.

The mITT population was used for the analysis of the primary efficacy endpoint. For the secondary analyses the full ITT population was used. The per-protocol population was used for a sensitivity analysis of the primary endpoint.

For the primary efficacy and other time-to-event variables, differences between treatment groups were tested using the proportional hazards model with treatment and centre as explanatory variables. Ninety-five percent confidence intervals for the hazard ratios were provided.

Adverse events (AEs) were summarised descriptively for each treatment by system organ class (SOC) and preferred term.

Results
A total of 1421 patients were screened, of whom 1376 were randomised. Approximately a half of patients did not experience prodromal symptoms during the study and therefore discontinued without taking study drug. The discontinuation rate in those patients that took study drug was similar in all treatment groups and was due to protocol violations, administrative problems, patients lost to follow-up, withdrawal of patient consent and AEs. The number of patients excluded from the per-protocol population was comparable between treatment groups. The most frequent major protocol violations were ‘first dose taken more than 1 hour after onset of prodrome’, ‘patient non-compliant with study drug dosing’ and ‘2nd dose >18 hours post 1st dose’.

Primary endpoint
For the modified ITT population, the time to healing was significantly reduced in the famciclovir treatment groups compared to placebo. The median time to healing for patients in the famciclovir 1500 mg q.d. and 750 mg b.i.d. groups was 1.8 and 2.2 days shorter, respectively, than in the placebo group. The hazard ratios for time to healing were statistically significant in favour of the two famciclovir groups. Similar results were observed in the per-protocol population.

The baseline demographics were similar between the treatment groups. There were however, very few non-Caucasian patients enrolled in the study.

The proportion of patients with virological confirmation was low and does not allow the drawing of conclusions on the effect of treatment e.g. on viral shedding.
**Famciclovir 500 mg film-coated tablets**  
**UK/H/4775/001/DC**

### Primary efficacy results (time to healing of primary lesion complex, mITT and PP populations)

<table>
<thead>
<tr>
<th>Variable Population</th>
<th>Statistic</th>
<th>Famciclovir 1500 mg q.d.</th>
<th>Famciclovir 750 mg b.i.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to healing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modifed ITT</td>
<td>N</td>
<td>152</td>
<td>157</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Q1 (days)</td>
<td>2.8</td>
<td>2.7</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Median (days)</td>
<td>4.4</td>
<td>4.0</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>95% CI median time¹</td>
<td>(3.8, 5.0)</td>
<td>(3.4, 4.6)</td>
<td>(5.5, 6.9)</td>
</tr>
<tr>
<td></td>
<td>Q3 (days)</td>
<td>6.5</td>
<td>6.2</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Difference in median (famciclovir-placebo)</td>
<td>-1.8</td>
<td>-2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI of difference (famciclovir-placebo)</td>
<td>(-2.7, -0.9)</td>
<td>(-3.1, -1.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hazard ratio vs placebo²</td>
<td>1.64</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value³</td>
<td>&lt;0.001⁴</td>
<td>&lt;0.001⁴</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI of hazard ratio</td>
<td>(1.26, 2.14)</td>
<td>(1.58, 2.66)</td>
<td></td>
</tr>
</tbody>
</table>

| Per-protocol         | N         | 121                      | 126                      | 128     |
|                      | Q1 (days) | 2.8                      | 2.6                      | 4.4     |
|                      | Median (days) | 4.4                  | 4.0                      | 6.1     |
|                      | 95% CI median time¹ | (3.8, 5.0)     | (3.5, 4.5)               | (5.3, 7.0)               |
|                      | Q3 (days) | 6.5                      | 6.4                      | 8.4     |
|                      | Difference in median (famciclovir-placebo) | -1.7                  | -2.1                     |         |
|                      | 95% CI of difference (famciclovir-placebo) | (-2.8, -0.7)     | (-3.1, -1.2)             |         |
|                      | Hazard ratio vs placebo² | 1.71                  | 2.06                     |         |
|                      | p-value³ | <0.001⁴                  | <0.001⁴                 |         |
|                      | 95% CI of hazard ratio | (1.28, 2.29)     | (1.55, 2.73)             |         |

¹ Based on first-order Taylor series approximation of standard errors
² Based on proportional hazards model with treatment and centre as explanatory variables
³ For hazard ratios for each famciclovir treatment group versus placebo
⁴ Statistically significant at 5% level based on Hochberg multiple testing procedure comparing each famciclovir treatment to placebo

Source: [SCE-Table 3-5]

### Kaplan-Meier plot of time to healing of primary lesion complex (mITT population)

![Kaplan-Meier plot of time to healing of primary lesion complex (mITT population)](image)
In summary, the primary endpoint was met for both treatment groups when compared to placebo both in the mITT (primary analysis set) and the PP population. Median time to loss of crust was reduced from 6.2 to 4.4 days in the 1 x 1500 mg group and to 4.0 days in the 2 x 750 mg group. No significant difference was seen between the two dose regimens. The reduction of time to loss of crust as a measure of time to healing of 1.8/ 2.2 days is considered clinically relevant, and statistically significant for both regimens (p< 0.001), meeting the more stringent statistical requirements for a single pivotal study. The findings can also be considered robust to the choice of censoring method for handling withdrawals and missing data.

The primary analysis set for the secondary endpoints was the ITT population. The secondary efficacy endpoint “healing of all lesions” was met for both investigated famciclovir treatment regimens.

Time to healing of all lesions (primary and secondary vesicular lesions and aborted lesions) in the ITT population for the famciclovir 1500 mg q.d. and 750 mg b.i.d. groups was 1.4 and 1.2 days shorter, respectively, than for the placebo group. As aborted lesions were assigned a time of zero and the proportion of aborted lesions did not differ relevantly between treatment groups, these endpoints do not provide further information.

The endpoints “time to return to normal skin” and “time to resolution of pain” were statistically significantly superior to placebo only for the 1500 mg single dose regimen, (though positive trends were seen in the 750 mg b.i.d group). With the single dose regimen, median time to return to normal skin was reduced by 2.5 days (from 7 to 4.5) compared to placebo. For time to resolution of pain 1500 mg q.d. was superior to 750 mg b.i.d.

The overall result of the study provides evidence that famciclovir in a total dose of 1500 mg given for one day is effective in shortening the time to healing of recurrent herpes labialis lesions in immunocompetent adults.

**Supportive study**
This was an open-label phase IV observational study to evaluate oral Famvir (famciclovir) single-dose efficacy and safety in immunocompetent adults with recurrent herpes labialis. The primary objective was to assess the time to healing of all non-aborted labialis herpes lesions.

Patients were treated with famciclovir 1500 mg (single dose, 3 x 500 mg tablets) within 1 h of onset of prodromal active symptoms associated with a recurrent episode of herpes labialis. Primary outcome was time to healing of all non-aborted labialis herpes lesions (complete loss of crust and re-epithelialisation).

Secondary outcomes were similar to those in the pivotal study. Patient and investigator provided a subjective opinion on therapy results using a 4-point scale (1-4) at final visit.

The efficacy analyses were performed for the intent-to-treat (ITT) population. All statistical analyses were carried out at a 0.05 significance level. Statistical analyses are performed using only available data, missing values were not imputed.

**Results**
Out of 484 enrolled patients, 474 patients (97.9%) completed the study at the final visit, 10 (2.1%) patients discontinued the study. The mean time from onset of prodromal symptoms to
initiation of Famvir therapy was estimated at 11.0±17.98 hours (the median time = 3.25; from 0 up to 125.08 hours).

For all patients included in the efficacy analysis (n=480), the mean time from initiation of famciclovir therapy to re-epithelialization was estimated at 4.4±2.1 days (median = 4.5; from 1.5 up to 12.5 days).

The mean time from initiation of famciclovir therapy to resolution of lesion-associated prodromal symptoms was estimated 2.2±0.9 days (the median time = 2.5; from 1.5 up to 8.5 days).

For patients with the papule (vesicular) stage the mean time from initiation of famciclovir therapy to resolution of vesicles was estimated at 3.5±1.5 days (median = 3.5; from 1.5 up to 10.5 days).

The proportion of patients who developed the papule (vesicular) stage was 53.5% (259) patients.

Efficacy and tolerability estimates were available for 477 (98.6%) patients. Investigators estimated efficacy as “excellent” for 364 (75.2%) patients, as “good” for 99 (20.5%) patients and “fair” for 14(2.9%) patients.

Patients estimated efficacy as “excellent” in 369 (76.2%) cases, as “good” in 94 (19.4%) cases, “fair” in 12(2.5%) cases and “poor” in 2 (0.4%) cases.

The MAH concluded that the results of this study indicate that Famvir treatment in daily routine out-patient practice exhibits rapid and high efficacy and is well tolerated. The mean time from initiation of famciclovir therapy to re-epithelialisation was estimated at 4.4±2.1 days, the mean time from initiation of famciclovir therapy to resolution of lesion-associated prodromal symptoms was estimated to be 2.2±0.9 days. For patients with the papule stage the mean time from initiation of famciclovir therapy to resolution of vesicles was estimated at 3.5±1.5 days. Only one AE was registered in the study, which was considered unlikely to be related to famciclovir use.

In summary, in this observational study performed in several centres only the one day single dose treatment (1500 mg) was investigated. The median time to reach the primary outcome (complete loss of crust and re-epithelialisation) was 4.5 days and was, thus, in line with the time observed in the pivotal study, although the endpoint definition was slightly different from that study. The results of this observational study provide some supporting evidence for the claimed indication, although the lack of a placebo or comparator arm makes interpretation difficult.

Of interest, patients’ and investigators’ evaluation of the efficacy and tolerability of the treatment were evaluated as secondary endpoints. 97% of patients and investigators rated the efficacy as good or excellent. The high number of aborted lesions (only 53.5% developed vesicular lesions) in this study does however raise concerns that, in a number of cases, symptoms may have been misinterpreted as prodromal, presumably as patients were not correctly instructed in recognising the symptoms. This would have likely led to an over-enthusiastic evaluation of treatment.

Of note, the time to initiation of treatment was considerably longer than reported for the pivotal study. The mean time from onset of prodromi to start of treatment is reported to be 11
h, with a median of 3.25 h. The applicant did not consider it possible to evaluate what effect the time of treatment administration relative to the onset of prodromal symptoms may have had on the study outcomes.

### IV.5 Clinical safety

**Introduction**

The key safety population was the safety populations of the three studies conducted by the applicant involving immunocompetent adults with a history of recurrent herpes labialis as well as the three studies reported in the literature involving immunocompetent adults with a history of recurrent genital herpes.

The studies were not combined as the disease characteristics of the populations and dosing were not compatible.

There were no notable differences in the baseline demographics between the treatment groups in the recurrent herpes labialis population or between the treatment groups in the recurrent genital herpes population.

**Summary of trials which contributed safety data**

<table>
<thead>
<tr>
<th>Study objective</th>
<th>Treated patients</th>
<th>Safety population</th>
<th>Treatment duration</th>
<th>Dosage</th>
<th>Type of control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal controlled efficacy trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy and safety of famciclovir in recurrent herpes labialis infection</td>
<td>701</td>
<td>254</td>
<td>1 day</td>
<td>placebo famciclovir 1500 mg q.d. famciclovir 750 mg b.i.d.</td>
<td>double-blind, placebo controlled</td>
</tr>
<tr>
<td><strong>Open label trials in RHL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy and safety of famciclovir in recurrent herpes labialis infection</td>
<td>484</td>
<td>484</td>
<td>1 day</td>
<td>famciclovir 1500 mg q.d.</td>
<td>open label, no control</td>
</tr>
<tr>
<td>Safety and PK of famciclovir in recurrent herpes labialis infection in adolescents</td>
<td>53</td>
<td>53</td>
<td>1 day</td>
<td>famciclovir 1500 mg q.d.</td>
<td>open label, no control</td>
</tr>
<tr>
<td><strong>Randomized controlled trials of a one-day treatment in RGH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy and safety of famciclovir in recurrent genital herpes infection</td>
<td>328</td>
<td>186</td>
<td>1 day</td>
<td>placebo famciclovir 1000 mg b.i.d.</td>
<td>double-blind, placebo controlled</td>
</tr>
<tr>
<td>Efficacy and safety of famciclovir in recurrent genital herpes infection</td>
<td>756</td>
<td>371</td>
<td>1 day</td>
<td>famciclovir 1000 mg b.i.d valaciclovir 500 mg b.i.d. for 3 days</td>
<td>double-blind, active controlled</td>
</tr>
<tr>
<td>Efficacy and safety of famciclovir in recurrent genital herpes infection</td>
<td>304</td>
<td>98</td>
<td>1 day</td>
<td>placebo famciclovir 1000 mg b.i.d.</td>
<td>double-blind, placebo controlled</td>
</tr>
</tbody>
</table>

Reference: [Table listing of all clinical studies]}

The pivotal study with the relevant population of patients for the indication sought provides information on AEs. Subgroup analyses including age group, region, gender and race were also performed for this study.
Patient exposure
A summary of the overall duration of exposure for the populations with the target indications of recurrent herpes labialis and recurrent genital herpes is presented below. Patients received the complete famciclovir dose during a one-day period. The majority of patients in both populations took a total number of two doses during the study. All patients in the two open studies received a single dose of 1500 mg. The overall drug exposures for all studies supporting the safety claims are presented. A total of 1724 patients were exposed to \( \geq 1500 \) mg/day total dose and 740 were exposed to \( > 2000 \) mg/day.

Summary of exposure - exposure in one-day treatment efficacy population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Daily Dose (mg)</th>
<th>RHL population N = 1138</th>
<th>RGH population N = 1489</th>
<th>Total population N = 2627</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCV mg 750 mg b.i.d.</td>
<td>1500</td>
<td>220</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>FCV 1500 mg q.d.</td>
<td>1500</td>
<td>764</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>FCV 1000 mg q.d.</td>
<td>2000</td>
<td>-</td>
<td>-</td>
<td>740</td>
</tr>
<tr>
<td>VACV 500 mg b.i.d.</td>
<td>1000</td>
<td>-</td>
<td>-</td>
<td>385</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>254</td>
<td>21</td>
<td>364</td>
</tr>
</tbody>
</table>

Disc. Represents the number of patients discontinued from the study regardless of reason
FCV=famciclovir; ACV=aciclovir; VACV=valaciclovir
RHL=Recurrent herpes labialis; RGH=Recurrent genital herpes

Source: [SCS-Table 1-2]

The primary SOC most affected by AEs overall was nervous system disorders and the rate was higher in the famciclovir 1000 mg b.i.d. group compared to the other treatment groups.

The next most frequently affected organ class was gastrointestinal disorders, the rates of which were similar between all treatment groups except for the famciclovir 1500 mg q.d. group where the rate was slightly lower. The overall pattern of AEs is similar to that seen with current dosing regimens, which utilise lower daily doses and longer treatment periods.

Most frequently affected system organ classes among all adverse events
The overall rates of AEs and of drug-related AEs were similar for famciclovir 1500 mg q.d., famciclovir 750 mg b.i.d., famciclovir 1000 mg b.i.d., valaciclovir 500 mg b.i.d. and placebo groups.

The overall incidence of AEs and most frequently affected system organ classes in the safety population of patients with recurrent genital herpes and recurrent herpes labialis in the two large placebo-controlled studies (the randomised, double-blind, placebo-controlled study in patients with recurrent genital herpes and the pivotal study) is presented for each treatment group in the table below. The proportion of patients reporting AEs was higher in the famciclovir treatment groups compared to the placebo groups although no consistent differences were observed for specific AEs within the different SOC.
Famciclovir 500 mg film-coated tablets

UK/H/4775/001/DC

Adverse event incidence overall and by system organ class and preferred term in the placebo controlled studies

<table>
<thead>
<tr>
<th>System organ class affected</th>
<th>Famciclovir 1000 mg b.i.d.</th>
<th>Placebo</th>
<th>Famciclovir 1500 mg q.d.</th>
<th>Placebo</th>
<th>Famciclovir 750 mg b.i.d.</th>
<th>Placebo</th>
<th>Recurrent Genital Herpes</th>
<th>Recurrent Herpes Labialis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>24 (14.7)</td>
<td>13 (7.8)</td>
<td>24 (10.6)</td>
<td>18 (8.2)</td>
<td>24 (9.4)</td>
<td>18 (8.2)</td>
<td>43 (26.4)</td>
<td>40 (24.1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>18 (9.8)</td>
<td>17 (10.2)</td>
<td>14 (6.2)</td>
<td>18 (8.2)</td>
<td>23 (9.1)</td>
<td>23 (9.1)</td>
<td>63 (27.8)</td>
<td>63 (27.8)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>5 (3.1)</td>
<td>3 (1.8)</td>
<td>6 (2.6)</td>
<td>6 (2.7)</td>
<td>5 (2.0)</td>
<td>5 (2.0)</td>
<td>54 (24.5)</td>
<td>54 (24.5)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>4 (2.5)</td>
<td>3 (1.8)</td>
<td>2 (0.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>53 (20.9)</td>
<td>53 (20.9)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>4 (2.5)</td>
<td>3 (1.8)</td>
<td>2 (0.9)</td>
<td>3 (1.4)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3 (1.8)</td>
<td>9 (5.4)</td>
<td>13 (5.7)</td>
<td>6 (2.7)</td>
<td>10 (3.9)</td>
<td>10 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>2 (1.2)</td>
<td>2 (1.2)</td>
<td>8 (3.5)</td>
<td>8 (3.6)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2 (1.2)</td>
<td>3 (1.8)</td>
<td>2 (0.9)</td>
<td>5 (2.3)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>2 (1.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0</td>
<td>0</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>0</td>
<td>3 (1.8)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0</td>
<td>3 (1.8)</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>0</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The primary SOC most affected by AEs overall was nervous system disorders and the rate was higher in the famciclovir 1000 mg b.i.d. group compared to the other treatment groups. The next most frequently affected organ class was gastrointestinal disorders, the rates of which were similar between all treatment groups except for the famciclovir 1500 mg q.d. group where the rate was slightly lower. The overall pattern of AEs is similar to that seen with current dosing regimens, which utilise lower daily doses and longer treatment periods.

**Most frequently occurring adverse events**

In all studies, headache was the most frequently reported AE and is listed as an undesirable event in the current label. The majority of famciclovir-treated patients with headache were female (a reflection of the demographics in the studies) and less than 65 years old. The headaches were mostly mild in intensity, were not recurrent, generally started on treatment (Day 0 or 1) and were short in duration. Many patients did not use concomitant medication to treat their headache. No headache was reported as an SAE in any of these studies.

The incidence of diarrhoea was higher in the famciclovir 1000 mg b.i.d. group compared to the other groups. Other AEs occurred at a similar rate in all treatment groups.
The majority of AEs with famciclovir in these studies were mild or moderate in severity. Headache was the only AE for which severe events occurred and the rates were comparable between the famciclovir- and placebo-treated patients.

**Deaths and other serious or clinically significant adverse events**

There were five treatment-emergent SAEs in the studies. None were reported in the studies in recurrent herpes labialis.

In the controlled study comparing famciclovir with valaciclovir in patients with recurrent genital herpes, the SAEs during treatment period were experienced by one patient of the valaciclovir group and by two patients of the famciclovir group. These SAEs were myocardial ischemia (famciclovir group), suicide attempt (famciclovir group), and suicide attempt (valaciclovir group).

In the study reported in the literature involving black patients with recurrent genital herpes, one patient had an SAE of palpitations during the treatment period on Day 1 that resolved on Day 2. The event was not suspected to be related to study medication and the patient was permanently discontinued due to the SAE.

SAEs during the follow-up period of this study were reported by one patient (0.5%) in the famciclovir group and one patient (1.0%) in the placebo group. Neither event was suspected to be related to study medication.

**IV.6 Risk Management Plan**

The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

The applicant has submitted a Risk Management Plan according to the format specified in GVP module V. This is acceptable.

**Conclusion**

All product literature (SmPC, PIL and labelling) is clinically acceptable. The SmPC is consistent with that for the reference product, apart from differences related to the additional indication. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with the current guidelines.

A Clinical Overview written by an appropriately qualified physician has been provided and is a satisfactory summary of the clinical aspects of the dossier.

The grant of a Marketing Authorisation is recommended.

**V User consultation**

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
VI Overall conclusion, benefit/risk assessment and recommendation

Quality
The important quality characteristics of Famciclovir 500 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical
No new non-clinical data were submitted and none are required for applications of this type. The results of the environmental risk assessment (ERA) show that there is no increased risk to the environment from the use of famciclovir.

Clinical
The clinical data provides evidence that famciclovir in a total dose of 1500 mg given for one day is effective in shortening the time to healing of recurrent herpes labialis lesions in immunocompetent adults. As biowaiver criteria have been met, it can be accepted that Famciclovir 500 mg film-coated tablets are bioequivalent to the tablets used in the pivotal efficacy study.

The safety profile of famciclovir is well-known. No new or unexpected safety concerns arose from the studies conducted.

Benefit/risk assessment
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with famciclovir is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product is available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling texts are located in Annex 1, below.
Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) To delete Varicella zoster virus (VZV) infections herpes zoster, and Herpes simplex virus (HSV) infections genital herpes from the therapeutic indications of Famciclovir, 500 mg due to business reasons. (2) As a consequence, to remove pack sizes: 14, 21, 30, 50 and 56 tablets per blister. The SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3, 6.5, labelling and PIL have been updated consequentially.</td>
<td>UK/H/4775/001/IB/001/G</td>
<td>Y</td>
<td>04 February 2015</td>
<td>13 July 2015</td>
<td>Approval</td>
<td>Y (Annex 1)</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 00030/0448-0010
Product: Famciclovir 500 mg Film-coated tablets
Marketing Authorisation Holder: Novartis Consumer Health UK Limited
Active Ingredient(s): Famciclovir

Reason: (1) To delete Varicella zoster virus (VZV) infections herpes zoster, and Herpes simplex virus (HSV) infections genital herpes from the therapeutic indications of Famciclovir, 500 mg due to business reasons. (2) As a consequence, to remove pack sizes: 14, 21, 30, 50 and 56 tablets per blister. The SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3, 6.5, labelling and PIL have been updated consequentially.

Supporting Evidence: Updated SmPC, PIL and labels provided

Evaluation: These are satisfactory. The updated SmPC and PIL are available on the Medicines and Healthcare products Regulatory Agency website. The updated labels are presented below.
**Labelling text for Famciclovir 500 mg film-coated tablets**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Famciclovir 500 mg film-coated tablets
   
   Famciclovir

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   One film-coated tablet contains 500 mg famciclovir

3. **LIST OF EXCIPIENTS**
   
   Contains lactose anhydrous. See package leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Film-coated tablets
   
   3 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
Famciclovir 500 mg film-coated tablets

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Consumer Health UK Limited
Camberley GU15 3YL

12. MARKETING AUTHORISATION NUMBER(S)

PL 00030/0448

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famiclovir 500 mg film-coated tablets</td>
</tr>
<tr>
<td>fanciclovir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Consumer Health UK Limited</td>
</tr>
<tr>
<td>Camberley GU15 3YL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 25°C.</td>
</tr>
</tbody>
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<th>4. BATCH NUMBER</th>
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