Public Assessment Report

Decentralised Procedure

Famciclovir 125 mg Film-coated Tablets
Famciclovir 250 mg Film-coated Tablets
Famciclovir 500 mg Film-coated Tablets

PL 08137/0239
PL 08137/0240
PL 08137/0241
UK/H/2109/001/DC
UK/H/2109/002/DC
UK/H/2109/003/DC

Neolab Ltd
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Neolab Ltd Marketing Authorisations (licences) for the medicinal products Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets (product licence numbers: PL 08137/0239-0241) on 27 July 2011. These medicines are available on prescription only.

Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets stop viruses from reproducing and are used to treat the following types of infection in adults:

- Shingles (herpes zoster), which is an infection caused by a virus called varicella zoster (the same virus that causes chickenpox). Famciclovir stops the virus from spreading in the body so that healing can occur faster.
- Shingles in the area around the eye or of the eye itself (ophthalmic zoster).
- Genital herpes. Genital herpes is a viral infection caused by herpes simplex virus type 1 or 2. It is normally spread by sexual contact. It causes blisters and burning or itching around the genitals, which may be painful.

The data submitted in support of these applications for Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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1 Introduction
2 Quality aspects
3 Preclinical aspects
4 Clinical aspects
5 Overall conclusions
### Module 1

**Information about Decentralised Procedure**

| Names of the products in the Reference Member State | Famciclovir 125 mg Film-coated Tablets  
Famciclovir 250 mg Film-coated Tablets  
Famciclovir 500 mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Type of application</td>
<td>Generic (Article 10.1)</td>
</tr>
<tr>
<td>Name of the drug substance</td>
<td>Famciclovir</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antivirals for systemic use/ nucleosides and nucleotides excluding reverse transcriptase inhibitors (J05AB09)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Film-coated tablets; 125, 250 and 500 mg</td>
</tr>
</tbody>
</table>
| Reference numbers for the Decentralised Procedure   | UK/H/2109/001/DC  
UK/H/2109/002/DC  
UK/H/2109/003/DC |
| Reference Member State                              | United Kingdom                                                                   |
| Member States concerned                             | Ireland                                                                         |
| Start date of Decentralised Procedure               | 11 June 2008                                                                     |
| End date of Decentralised Procedure                 | 29 March 2011                                                                    |
| Marketing Authorisation numbers                     | PL 08137/0239  
PL 08137/0240  
PL 08137/0241 |
| Name and address of the Marketing Authorisation Holder | Neolab Ltd  
57 High Street  
Odiham  
Hants RG29 1LF  
UK |
Module 2

Summaries of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Famciclovir 125 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 125 mg famciclovir.

Each tablet contains 11 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Famciclovir 125 mg tablets are white to off-white coloured, circular, biconvex film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Varicella zoster virus (VZV) infections – herpes zoster
Famciclovir is indicated for
- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4)
- the treatment of herpes zoster in immunocompromised adults (see section 4.4)

Herpes simplex virus (HSV) infections – genital herpes
Famciclovir is indicated for
- 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

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

4.2 Posology and method of administration
Herpes zoster in immunocompetent adults
500 mg three times daily for seven days.
Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

**Herpes zoster in immunocompromised adults**
500 mg three times daily for ten days.
Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

**Genital herpes in immunocompetent adults**
First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

**Recurrent genital herpes in immunocompromised adults**
Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults
250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

**Suppression of recurrent genital herpes in immunocompromised adults**
500 mg twice daily.

**Patients with renal impairment**
Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

Table 1 Dose recommendations for adult patients with renal impairment

<table>
<thead>
<tr>
<th>Indication and nominal dose regimen</th>
<th>Creatinine clearance [ml/min]</th>
<th>Adjusted dose regimen</th>
</tr>
</thead>
</table>
| **Herpes zoster in immunocompetent adults**
500 mg three times daily for 7 days | | |
<p>| ≥ 60 | 500 mg three times daily for 7 days |
| 40 to 59 | 500 mg twice daily for 7 days |
| 20 to 39 | 500 mg once daily for 7 days |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpes zoster in immunocompromised adults</strong></td>
<td>≥ 60</td>
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<td>500 mg once daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>&lt; 20</td>
<td>250 mg once daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>Haemodialysis patients</td>
<td>250 mg following each dialysis during 7 days</td>
</tr>
<tr>
<td><strong>Genital herpes in immunocompetent adults – first episode of genital herpes</strong></td>
<td>≥ 40</td>
<td>250 mg three times daily for 5 days</td>
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<tr>
<td></td>
<td>20 to 39</td>
<td>250 mg twice daily for 5 days</td>
</tr>
<tr>
<td></td>
<td>&lt; 20</td>
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<tr>
<td>----------------------------------------------------------</td>
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</tr>
<tr>
<td>Haemodialysis patients</td>
<td></td>
<td>250 mg following each dialysis</td>
</tr>
</tbody>
</table>

Patients with renal impairment on haemodialysis
Since 4 h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly patients (≥ 65 years)
Dose modification is not required unless renal function is impaired.

Children and adolescents
Famciclovir is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Method of administration
Famciclovir can be taken without regard to meals (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use
Use in patients with renal impairment
In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

Use in patients with hepatic impairment
Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

Use for zoster treatment
Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to
intravenous antiviral therapy when response to oral therapy is considered insufficient.
Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.
Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes
Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

Other
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on famciclovir
No clinically significant interactions have been identified. Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination. Therefore, patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifen has been shown to be a potent inhibitor of this enzyme in vitro. Co-administration of raloxifene could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifen is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

4.6 Pregnancy and lactation

Pregnancy
There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific foetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.
Lactation
It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If the woman’s condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

Fertility
Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famciclovir should refrain from driving or operating machinery.

4.8 Undesirable effects
Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during postmarketing.

A total of 1,587 patients have received famciclovir at recommended doses in placebo- (n=657) and active- (n=930) controlled studies. These clinical studies were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. For adverse reactions which have never been observed in these studies, the upper limit of the 95% confidence interval is not expected to be higher than 3/X (based on the “rule of three”), with X representing the total sample size (n=1,587). Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Adverse reactions
<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Rare: Thrombocytopenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon: Confusion</td>
<td></td>
</tr>
<tr>
<td>Rare: Hallucinations</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common: Headache</td>
<td></td>
</tr>
<tr>
<td>Common: Dizziness, somnolence</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Nausea, vomiting.</td>
<td></td>
</tr>
<tr>
<td>Rare: Vomiting.</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Abnormal liver function tests</td>
<td></td>
</tr>
<tr>
<td>Rare: Cholestatic jaundice.</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Rash, pruritus</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Urticaria, serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)</td>
<td></td>
</tr>
</tbody>
</table>

*Never reported in clinical trials; category is based on the “rule of three”*

Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

4.9 **Overdose**

Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 h haemodialysis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: JO5AB09

*Mechanism of action*

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 virus 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.

**Resistance**

Like aciclovir, the most common form of resistance encountered among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would generally be expected to be cross-resistant to both penciclovir and aciclovir.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients.

**Clinical efficacy**

In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one active controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients. Placebo-controlled and uncontrolled studies of up to 16 weeks duration showed that famciclovir was effective in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

**5.2 Pharmacokinetic properties**

**General characteristics**

**Absorption**
Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and 5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose. Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

**Distribution**
Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins.

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

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

**Characteristics in special populations**

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

**Subjects with renal impairment**
The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal impairment (see section 4.2).

**Subjects with hepatic impairment**
Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir.
**Elderly patients (≥ 65 years)**
Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2).

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

5.3 **Preclinical safety data**

**General toxicity**
Studies on safety pharmacology and repeated dose toxicity reveal no special hazard for humans.

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

**Carcinogenicity**
At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

**Reproductive toxicity**
Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats given 500 mg/kg/day. Furthermore, degenerative changes of the testicular epithelium were noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Tablet core:**
Lactose monohydrate  
Croscarmellose sodium  
Crospovidone  
Magnesium stearate

**Tablet coat:**
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions. Store in the original packaging.

6.5 **Nature and contents of container**
Famciclovir 125 mg Tablets are packed in a blister strip of PVC/PVdC film and aluminum foil.

Pack sizes of 10 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORITYHOLDER**
Neolab Ltd
57 High Street
Odiham
Hants
RG29 1LF
UK

8 **MARKETING AUTHORIZATION NUMBER(S)**
PL 08137/0239

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**
27/07/2011

10 **DATE OF REVISION OF THE TEXT**
27/07/2011
1 NAME OF THE MEDICINAL PRODUCT
Famciclovir 250 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 250 mg famciclovir.

Each tablet contains 22 mg lactose.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Famciclovir 250 mg tablets are white to off-white coloured, circular, biconvex film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Varicella zoster virus (VZV) infections – herpes zoster
Famciclovir is indicated for
- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4)
- the treatment of herpes zoster in immunocompromised adults (see section 4.4)

Herpes simplex virus (HSV) infections – genital herpes
Famciclovir is indicated for
- 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

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

4.2 Posology and method of administration
Herpes zoster in immunocompetent adults
500 mg three times daily for seven days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Herpes zoster in immunocompromised adults
500 mg three times daily for ten days.
Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Genital herpes in immunocompetent adults
First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Recurrent genital herpes in immunocompromised adults
Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults
250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

Suppression of recurrent genital herpes in immunocompromised adults
500 mg twice daily.

Patients with renal impairment
Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

Table 1 Dose recommendations for adult patients with renal impairment

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<tr>
<th>Indication and nominal dose regimen</th>
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<th>Adjusted dose regimen</th>
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</thead>
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<td>Age Range</td>
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< 20 | 125 mg once daily  

| Haemodialysis patients | 125 mg following each dialysis  

## Suppression of recurrent genital herpes in immunocompromised adults

### 50 mg twice daily

| ≥ 40 | 500 mg twice daily  
| 20 to 39 | 500 mg once daily  
| < 20 | 250 mg once daily  

| Haemodialysis patients | 250 mg following each dialysis  

Patients with renal impairment on haemodialysis
Since 4 h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly patients (≥ 65 years)
Dose modification is not required unless renal function is impaired.

Children and adolescents
Famciclovir is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Method of administration
Famciclovir can be taken without regard to meals (see section 5.2).

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to penciclovir.

### 4.4 Special warnings and precautions for use

#### Use in patients with renal impairment

In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

#### Use in patients with hepatic impairment

Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

#### Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient. Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and
cerebrovascular complications should be treated with intravenous antiviral therapy.
Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

**Transmission of genital herpes**
Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

**Other**
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Effects of other medicinal products on famciclovir**
No clinically significant interactions have been identified. Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination. Therefore, patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifen has been shown to be a potent inhibitor of this enzyme in vitro. Co-administration of raloxifene could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifen is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

### 4.6 Pregnancy and lactation

**Pregnancy**
There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific foetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.

**Lactation**
It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If
the woman’s condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

**Fertility**
Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily (see section 5.3).

### 4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famciclovir should refrain from driving or operating machinery.

### 4.8 Undesirable effects
Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during postmarketing.

A total of 1,587 patients have received famciclovir at recommended doses in placebo- (n= 657) and active- (n=930) controlled studies. These clinical studies were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. For adverse reactions which have never been observed in these studies, the upper limit of the 95% confidence interval is not expected to be higher than 3/X (based on the “rule of three”), with X representing the total sample size (n=1,587).

Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse reactions</th>
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<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Rare: Thrombocytopenia.</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Uncommon: Confusion</td>
</tr>
<tr>
<td></td>
<td>Rare: Hallucinations.</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Very common: Headache</td>
</tr>
<tr>
<td></td>
<td>Common: Dizziness, somnolence</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Common: Nausea, vomiting.</td>
</tr>
<tr>
<td></td>
<td>Rare: Vomiting.</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Common: Abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>Rare: Cholestatic jaundice.</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Common: Rash, pruritus</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Urticaria, serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)</td>
</tr>
</tbody>
</table>
Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

4.9 Overdose

Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 h haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: JO5AB09

Mechanism of action

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 virus 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.

Resistance

Like aciclovir, the most common form of resistance encountered among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would generally be expected to be cross-resistant to both penciclovir and aciclovir.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of
penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients.

**Clinical efficacy**

In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one active-controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients. Placebo-controlled and uncontrolled studies of up to 16 weeks duration showed that famciclovir was effective in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

### 5.2 Pharmacokinetic properties

**General characteristics**

**Absorption**

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and 5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose. Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

**Distribution**
Penciclovir and its 6-deoxy precursor are poorly (<20%) bound to plasma proteins.

**Metabolism and elimination**

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

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

**Characteristics in special populations**

**Patients with herpes zoster infection**

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

**Subjects with renal impairment**

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal impairment (see section 4.2).

**Subjects with hepatic impairment**

Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir.

**Elderly patients (≥65 years)**

Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2).

**Gender**

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

General toxicity
Studies on safety pharmacology and repeated dose toxicity reveal no special hazard for humans.

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

Carcinogenicity
At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

Reproductive toxicity
Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats given 500 mg/kg/day. Furthermore, degenerative changes of the testicular epithelium were noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Lactose monohydrate
Croscarmellose sodium
Crospovidone
Magnesium stearate

Tablet coat:
Opadry White:
Hypromellose
Titanium dioxide (E171)
Macrogol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Store in the original packaging.

6.5 Nature and contents of container
Famciclovir 250mg tablets are packed in blister strip of PVC/PVdC film and Aluminium foil.

Pack sizes of 15, 21 and 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Neolab Ltd
57 High Street
Odiham
Hants
RG29 1LF
UK

8 MARKETING AUTHORITY NUMBER(S)
PL 08137/0240

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
27/07/2011

10 DATE OF REVISION OF THE TEXT
27/07/2011
1 NAME OF THE MEDICINAL PRODUCT
Famciclovir 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 500 mg famciclovir.

Each tablet contains 44 mg lactose.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Famciclovir 500 mg tablets are white to off-white coloured, capsule shaped, biconvex film-coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Varicella zoster virus (VZV) infections – herpes zoster
Famciclovir is indicated for
- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4)
- the treatment of herpes zoster in immunocompromised adults (see section 4.4)

Herpes simplex virus (HSV) infections – genital herpes
Famciclovir is indicated for
- 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

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

4.2 Posology and method of administration
Herpes zoster in immunocompetent adults
500 mg three times daily for seven days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Herpes zoster in immunocompromised adults
500 mg three times daily for ten days.
Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Genital herpes in immunocompetent adults
First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Recurrent genital herpes in immunocompromised adults
Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults
250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

Suppression of recurrent genital herpes in immunocompromised adults
500 mg twice daily.

Patients with renal impairment
Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

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Haemodialysis patients & 125 mg following each dialysis

| Suppression of recurrent genital herpes in immunocompromised adults 50 mg twice daily | ≥ 40 | 500 mg twice daily |
| 20 to 39 | 500 mg once daily |
| < 20 | 250 mg once daily |
| Haemodialysis patients | 250 mg following each dialysis |

Patients with renal impairment on haemodialysis
Since 4 h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly patients (≥ 65 years)
Dose modification is not required unless renal function is impaired.

Children and adolescents
Famciclovir is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Method of administration
Famciclovir can be taken without regard to meals (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use
**Use in patients with renal impairment**
In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

**Use in patients with hepatic impairment**
Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

**Use for zoster treatment**
Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.
Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

**Transmission of genital herpes**

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

**Other**

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Effects of other medicinal products on famciclovir**

No clinically significant interactions have been identified.

Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination. Therefore, patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifen has been shown to be a potent inhibitor of this enzyme in vitro. Co-administration of raloxifene could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifen is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

### 4.6 Pregnancy and lactation

**Pregnancy**

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific foetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.

**Lactation**

It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If
the woman’s condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

**Fertility**
Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily (see section 5.3).

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famciclovir should refrain from driving or operating machinery.

### 4.8 Undesirable effects

Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during postmarketing.

A total of 1,587 patients have received famciclovir at recommended doses in placebo- (n= 657) and active- (n=930) controlled studies. These clinical studies were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. For adverse reactions which have never been observed in these studies, the upper limit of the 95% confidence interval is not expected to be higher than 3/X (based on the “rule of three”), with X representing the total sample size (n=1,587). Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2  Adverse reactions

<table>
<thead>
<tr>
<th><strong>Blood and lymphatic system disorders</strong></th>
<th>Rare: Thrombocytopenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon: Confusion</td>
<td></td>
</tr>
<tr>
<td>Rare: Hallucinations</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common: Headache</td>
<td></td>
</tr>
<tr>
<td>Common: Dizziness, somnolence</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Rare: Vomiting</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Abnormal liver function tests</td>
<td></td>
</tr>
<tr>
<td>Rare: Cholestatic jaundice</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common: Rash, pruritus</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Urticaria, serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)</td>
<td></td>
</tr>
</tbody>
</table>

MHRA PAR; FAMCICLOVIR 125 MG, 250 MG AND 500 MG FILM-COATED TABLETS, PL 08137/0239-0241
Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

4.9 Overdose
Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 h haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: JO5AB09

Mechanism of action
Famciclovir is the oral prodrug of penciclovir. Famciclovir is rapidly converted \textit{in vivo} into penciclovir, which has \textit{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 \textit{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 virus 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.

Resistance
Like aciclovir, the most common form of resistance encountered among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would generally be expected to be cross-resistant to both penciclovir and aciclovir.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of
penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients.

**Clinical efficacy**

In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one active-controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients. Placebo-controlled and uncontrolled studies of up to 16 weeks duration showed that famciclovir was effective in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

### 5.2 Pharmacokinetic properties

**General characteristics**

**Absorption**

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and 5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose. Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

**Distribution**

Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins.
**Metabolism and elimination**

Famiclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine. No unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours. Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

**Characteristics in special populations**

**Patients with herpes zoster infection**

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

**Subjects with renal impairment**

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal impairment (see section 4.2).

**Subjects with hepatic impairment**

Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir.

**Elderly patients (≥ 65 years)**

Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2).

**Gender**

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

### 5.3 Preclinical safety data

**General toxicity**
Studies on safety pharmacology and repeated dose toxicity reveal no special hazard for humans.

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

**Carcinogenicity**
At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

**Reproductive toxicity**
Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats given 500 mg/kg/day. Furthermore, degenerative changes of the testicular epithelium were noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Croscarmellose sodium
- Crospovidone
- Magnesium stearate

**Tablet coat:**
- Opadry White:
  - Hypromellose
  - Titanium dioxide (E171)
  - Macrogol.

#### 6.2 Incompatibilities
Not applicable.

#### 6.3 Shelf life
3 years.

#### 6.4 Special precautions for storage
This medicinal product does not require any special storage conditions. Store in the original packaging.
6.5 **Nature and contents of container**
Famciclovir 500 mg tablets are packed in blister strip of PVC/PVdC film and Aluminium foil.
Pack sizes of 14, 30 and 56 tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORITY HELDER**
Neolab Ltd
57 High Street
Odiham
Hants
RG29 1LF
UK

8 **MARKETING AUTHORIZATION NUMBER(S)**
PL 08137/0241

9 **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
27/07/2011

10 **DATE OF REVISION OF THE TEXT**
27/07/2011
PATIENT INFORMATION LEAFLET
FAMCICLOVIR 125, 250, 500 mg FILM-COATED TABLETS
(famciclovir)

The name of this medicine is Famciclovir 125, 250, 500 mg Film-Coated Tablets, which will be referred to as Famciclovir Tablets throughout this leaflet.

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT FAMCICLOVIR TABLETS ARE AND WHAT THEY ARE USED FOR

Famciclovir is an antiviral medicine. It stops the infecting virus from reproducing. Since the virus reproduces very early in the infection, you will benefit most from treatment if you take Famciclovir as soon as the first symptoms appear.

Famciclovir is used to treat two types of viral infections in adults:
- Shingles (herpes zoster), which is a viral infection caused by a virus called varicella zoster (the same virus that causes chickenpox).
- Genital herpes, which is a viral infection caused by the herpes simplex virus type 1 or 2. It is normally spread by sexual contact.

Famciclovir is also used for the treatment of shingles in the area around the eye or of the eye itself (ophthalmic zoster).
- Genital herpes. Genital herpes is a viral infection caused by herpes simplex virus type 1 or 2. It is normally spread by sexual contact. It causes blisters and burning or itching around the genitals, which may be painful. Famciclovir is used to treat genital herpes infections in adults. People who have frequent episodes of genital herpes can also take Famciclovir to help prevent the attacks.

2. BEFORE YOU TAKE FAMCICLOVIR TABLETS

Do not take Famciclovir Tablets:
- If you are allergic (hypersensitive) to Famciclovir, to any of the other ingredients listed in section 6, or to penciclovir (the active metabolite of famciclovir) and an ingredient of some other medicines.

Ask your doctor for advice, if you think you may be allergic.

Take special care with Famciclovir Tablets:
- If you have kidney problems (or have had them before). Your doctor may decide to give you a lower dose of Famciclovir Tablets.
- If you have problems with your body's immune system.
- If you have liver problems.

If any of these applies to you, tell your doctor before you take Famciclovir Tablets.

Children and adolescents below the age of 16 years.

Famciclovir is not recommended for use in children and adolescents.

Prevent passing genital herpes to others:
- If you are taking Famciclovir to treat or to suppress genital herpes, or if you have had genital herpes in the past, you should still practice safe sex, including the use of condoms. This is important to prevent you passing the infection on to others. You should not have sex if you have genital sores or blisters.

Taking other medicines:
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important that you tell your doctor or pharmacist if you are taking any of the following medicines:
- Valaciclovir (used to prevent and treat shingles).
- Probiclovir (used to treat high blood levels of uric acid associated with gout and to increase blood levels of penciclovir-type antibiotics), or any other medicine that can affect your kidneys.

Taking your medicine with food and alcohol:

You can take Famciclovir Tablets with or without food.

Pregnancy and breast-feeding:

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or think you may be, tell your doctor. Famciclovir is not to be used during pregnancy unless clearly necessary. Your doctor will discuss with you the possible risks of taking famciclovir during pregnancy.

If you are breast-feeding, tell your doctor. Famciclovir is not to be used during breast-feeding unless clearly necessary. Your doctor will discuss with you the possible risks of taking famciclovir during breast-feeding.

Driving and using machines:

In rare cases Famciclovir can cause dizziness, drowsiness or confusion. Do not drive or use machines if you have any of these symptoms while taking Famciclovir Tablets.

Important information about some of the ingredients of Famciclovir Tablets:

If you have been told by your doctor that you have an intolerance to some sugars, e.g. lactose, contact your doctor before taking this medicine. Famciclovir 125 mg, 250 mg, 500 mg tablets contain lactose.

3. HOW TO TAKE FAMCICLOVIR TABLETS

Always take famciclovir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- The daily dose and length of treatment will depend on the type of viral infection you have – see below. Your doctor will prescribe the correct dose for you.
- For the best results start the medicine as soon as possible after the first signs and symptoms appear.
- Do not have sexual contact with anyone if you have symptoms of genital herpes – even if you have started treatment with Famciclovir. This is because you could pass the herpes infection to your partner.
- If you have or have had kidney problems, your doctor may decide to give you a lower dose of famciclovir.

Dose for shingles:

If you have a normal immune system, the recommended dose is:
- one tablet of 500 mg, three times a day, for seven days.
- one tablet of 500 mg, three times a day, for ten days.

Dose for genital herpes:

The dose depends on the state of your immune system, and the stage of your infection.
- If you have a normal immune system, the dose is as follows:
- For the first episode, the recommended dose is:
  - one tablet of 250 mg three times a day, for five days.

- If you have taken famciclovir before to treat genital herpes:

- If you have a normal immune system, take one tablet of 500 mg three times a day, for one day.

- If you have had kidney problems, your doctor may decide to give you a lower dose of famciclovir.

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To treat oral and/or genital herpes, the recommended dose is:
- one tablet of 125 mg twice a day, for five days.
- one tablet of 250 mg twice a day.
Your doctor will tell you how long you need to continue taking your tablets.
- one tablet of 500 mg twice a day.
To prevent oral and/or genital herpes, the recommended dose is:
- one tablet of 125 mg twice a day.
- one tablet of 250 mg twice a day.
- one tablet of 500 mg twice a day.
Your doctor will tell you how long you need to continue taking your tablets.

If you have a reduced immune system, the doses are as follows:
To treat the current outbreak, the recommended dose is:
- one tablet of 125 mg twice a day, for seven days.
To prevent the current outbreak, the dose is:
- one tablet of 125 mg twice a day.

If you take more Famciclovir Tablets than you should:
- If you have taken more tablets than you have been told to take, or if someone else accidentally takes your medicine, go to your doctor or hospital for advice immediately. Show them your pack of tablets.

Taking too much Famciclovir may affect the kidneys. In people who already have kidney problems (for example, if you have had some kidney disease in the past, or have heart disease or diabetes) your kidneys may not work properly and you may have kidney failure. If your dose is not corrected lowered.

If you forget to take Famciclovir Tablets:
- If you forget to take a dose of Famciclovir, you should take it as soon as you remember. Then take your next dose as scheduled. However, do not take two doses within a time interval of less than 1 hour, in that case you should skip the missed dose. Furthermore, do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE-EFFECTS

Like all medicines, Famciclovir can cause side effects, although not everybody gets them. The side effects caused by Famciclovir are usually mild to moderate in intensity.

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 in 10 users)
- common (affects 1 to 10 users in 100 users)
- uncommon (affects 1 to 10 users in 1,000 users)
- rare (affects 1 to 10 users in 10,000 users)
- very rare (affects less than 1 in 10,000 users)

Serious side effects of Famciclovir are:
- Severe blurring of the vision or miosis (narrowing of the pupils), eye pain, nausea, vomiting, diarrhea, respiratory distress, shock, or renal failure.
- Unexplained bruising, redness, or purpura (purple spots on the skin or membranes) (these could be signs of a severe allergic skin reaction, for frequency see below).

Less common side effects:
- Headache
- Common cold symptoms
- Feeling sick (nausea)
- Vomiting
- Diarrhoea
- Rash
- Pruritus
- Liver function test giving abnormal results

Uncommon side effects:
- Confusion
- Severe skin reactions

Rare side effects:
- Mucositis (inflammation of the mouth and/or throat)
- Yellowing of the skin and/or eyes
- Low platelet count

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FAMCICOLOVIR TABLETS

- Keep out of the reach and sight of children.
- Do not use Famciclovir Tablets after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store your tablets in the original packaging.
- Do not use Famciclovir Tablets if you notice the pack is damaged or shows signs of tampering.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Famciclovir Tablets contain:
The active substance is Famciclovir.
They also contain: lactose monohydrate, croscarmellose sodium, crospovidone and magnesium stearate. The tablet contains Opadry White hydrotrope, talc, magnesium trisilicate, starch paste and dextrose.

What Famciclovir Tablets look like and contents of the pack:
Famciclovir Tablets are white to off-white, oval, delayed-release tablets (125mg & 250mg), capsule-shaped (500mg), biodegradable film-coated tablets plain on both sides.
Famciclovir 125 mg Tablets come in packs of 10 tablets.
Famciclovir 250 mg Tablets come in packs of 10, 28 or 56 tablets.
Famciclovir 500 mg Tablets come in packs of 14, 30 or 56 tablets.

Marketing Authorisation Holder and Manufacturer:
The marketing authorisation holder is Neoset Ltd, 57 High Street, Oldham, Lancashire, OL11 3LF, UK.
This information is available in alternative formats upon request.
This leaflet was last approved in April 2011.
Module 4

Labelling

PL 08137/0239

Blister:
**Famciclovir 250 mg Film-coated Tablets**
MA Holder: Neolab Ltd
XXXXXX
Code No.: XXORU095/XXX

**Famciclovir 250 mg Film-coated Tablets**
MA Holder: Neolab Ltd
XXXXXX
Code No.: XXORU095/XXX
PL 08137/0241

Blister:

Famciclovir 500 mg Film-coated Tablets
MA Holder: Neolab Ltd
XXXXXX
Code No. XXDXXXXX

Famciclovir 500 mg Film-coated Tablets
MA Holder: Neolab Ltd
XXXXXX
Code No. XXDXXXXX

Famciclovir 500 mg Film-coated Tablets
MA Holder: Neolab Ltd
XXXXXX
Code No. XXDXXXXX
Famciclovir 500 mg Film-coated Tablets

30 Film-coated Tablets

Each film-coated tablet contains:
- Famciclovir 500 mg
- Lactose monohydrate
- Microcrystalline cellulose
- Hydroxypropyl methylcellulose
- Titanium dioxide
- Stearic acid

For oral administration. Not for injection.

Not suitable for use during pregnancy and lactation.

For use in adults only.

For dispensing label.

PL 0817029-0241
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Famiclovir 125 mg, 250 mg and 500 mg Film-coated Tablets (PL 08137/0239-0241) in the treatment of herpes simplex and herpes zoster virus infections could be approved.

EXECUTIVE SUMMARY

Problem statement
These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that that the proposed products are generic versions of the products Famvir 125mg tablets (PL 00101/0625), Famvir 250mg tablets (PL 00101/0624) and Famvir 500mg tablets (PL 00101/0623) by Novartis Pharmaceuticals UK Ltd, first authorised in the UK on 10 December 1993. The reference products have, therefore, been authorised in the EEA for at least 10 years and the legal basis of these applications is acceptable.

With the UK as the RMS in this Decentralised Procedure, Neolab Ltd is applying for Marketing Authorisations for these products in Ireland.

An application for Famiclovir 750 mg Film-coated Tablets was initially included in this procedure. However, Famvir 125mg, 250mg, 500mg and 750mg tablets recently underwent Article 30 harmonisation, during which the decision to remove the indication for the 750 mg strength was taken, as the pharmacokinetic parameters were found to be unfavourable. Therefore, the Marketing Authorisation Holder decided to withdraw this product strength from the market and the Committee for Medicinal Products for Human Use (CHMP) also concluded that no generic versions of the 750mg strength product would be considered for Marketing Authorisation.

About the products
Famiclovir is the oral form of penciclovir. Famiclovir is rapidly converted in vivo into penciclovir, which has in vivo and in vitro activity against human herpes viruses, including varicella zoster virus and herpes simplex virus types 1 and 2. In virus-infected cells penciclovir is rapidly and efficiently converted into the 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. Therefore, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory
requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

**GMP**
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

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.

**GLP**
No new preclinical studies were submitted in support of these applications, and none are needed for an application of this type.

**GCP**
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practice (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

- **rINN:** Famciclovir
- **Chemical name:** 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediol diacetate

**Structure**

![Chemical structure of Famciclovir](image)
General Properties

Description: A white to off-white crystalline powder. Freely soluble in methanol and acetone, and sparingly soluble in water.

Molecular formula: $C_{14}H_{19}N_{5}O_{4}$

Relative molecular mass: 321.33

Polymorphism: Famciclovir exists in three polymorphic forms, designated as Forms I, II and III.

Synthesis of the drug substance from the designated starting material 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.

An appropriate specification is applied to the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.

Drug products

Famciclovir 125 mg and 250 mg Film-coated Tablets are white to off-white coloured, circular, biconvex film-coated tablets, plain on both sides. Famciclovir 500 mg Film-coated Tablets are white to off-white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides. These tablets contain the pharmaceutical excipients lactose monohydrate, croscarmellose sodium, crospovidone, magnesium stearate, opadry white, hypromellose, titanium dioxide (E171) and macrogol.

All excipients comply with their respective Ph. Eur. monograph, with the exception of Opadry White, which is controlled to in-house specifications. In the absence of a relevant monograph for this excipient, this is acceptable. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient of animal origin in the product is lactose. A statement is provided by the supplier of lactose confirming that it is in compliance with the requirements of the relevant guideline and Directives with regard to TSE.
**Pharmaceutical development**
The objective of the development programme was to develop a formulation similar to the innovator product, Famvir tablets. A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

**Manufacturing process**
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process.

Results from pilot scale batches show batch to batch consistency and suggest that the critical process parameters have been identified. The validation scheme to be followed for production batches will be the same as that for the pilot scale batches. Validation studies will be conducted on the first three production scale batches of the three tablet strengths and the results will be available for verification post authorisation.

**Finished product specifications**
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container closure system**
The finished products are stored in blister strips of PVC/PVdC film and aluminum foil. Each pack contains 10 tablets.

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

**Stability of the products**
Stability studies were performed in accordance with current guidelines on the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years when the storage precaution ‘Store in the original package’ is applied.

**Product literature**
The SmPCs, PILs and product labels are pharmaceutically acceptable.

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, as amended. 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.
Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Quality conclusion
There are no objections to the approval the Marketing Authorisation applications for Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets from a quality point of view.

Preclinical aspects

Preclinical overview
The pharmacological, pharmacokinetic and toxicological properties of famciclovir are well known. As famciclovir is a widely used, well known drug substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The preclinical overview has been written by an appropriately qualified expert. The overview is acceptable

Environmental risk assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of these generic products onto the market is unlikely to result in an increase in the combined sales of all famciclovir-containing products, which in turn is unlikely to increase exposure of the environment to famciclovir.

Product literature
The product literature is acceptable from a preclinical point of view.

Preclinical conclusion
There are no objections to the approval the Marketing Authorisation applications for Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets from a preclinical point of view.

Clinical aspects

Pharmacokinetics
To support the applications, an open label, single dose, balanced, randomised, two-treatment, two-period, two-sequence, crossover experimental evaluation of relative bioavailability of two formulations of famciclovir hydrochloride 750 mg tablets in healthy adult human male subjects under fasting conditions was conducted.

Test and reference products
Test Product (A): Famciclovir Tablets 750 mg

Reference Product (B): Famvir 750 mg (Famciclovir Tablets 750 mg)
Biowaiver
This Decentralised Procedure originally included four strengths of Famciclovir film-coated tablets: 125 mg, 250 mg, 500 mg, and 750 mg. The highest strength tablet was used in the bioequivalence study. Based on the dissolution profile and the linear pharmacokinetic profile up to the maximum strength of 750 mg, the request for biowaiver is acceptable. Although the 750 mg product strength is no longer proposed for Marketing Authorisation, the use of this product strength in the bioequivalence study is acceptable.

Population studied
Twenty eight healthy male volunteers with an age range from 18 to 45 years were entered in the study and 27 subjects completed the study.

Subjects were admitted at the clinical facility at least 10 hours prior to study drug administration and remained in the clinical trial site until 12 hours post-dosing. They were provided a meal at least 10 hours prior to dosing.

Dose administered (test/reference)
A single oral dose (750mg) of the assigned formulation in the fasting state was administered to each subject.

Duration of sampling following dosing
Serial blood samples were collected in each period at pre-dose and at intervals up to 12 hours following the drug administration in each period.

Sampling frequency around T_max
T_max for penciclovir, a metabolite of famciclovir, is around 2 hours in the fasting state and sampling frequency was sufficient for accurate C_max estimation.

Washout period
There was a washout period of 6 days between the two periods of the study and this was sufficient to avoid carryover as evidenced by undetectable levels in the pre-dose samples in period two.

Pre-defined bioequivalence acceptance criteria
Bioequivalence was to be concluded if the 90% Confidence Intervals for the ratios of the means of Ln-transformed pharmacokinetic parameters C_max, AUC_0-t, and AUC_0-∞, of penciclovir for the test and reference formulations were within the bioequivalence limits of 80%-125%. A widened range of 75-133% for C_max was to be considered if there was significant variation.

Analytical methods
Penciclovir was measured using a validated LC-MS-MS detection method.

Method of data analysis
Pharmacokinetic parameters (T_max, C_max, AUC_0-t, AUC_0-∞, lambda z, kel and t1/2) were calculated from the plasma penciclovir concentrations by non-compartmental analysis. The 90% Confidence Intervals for the ratios of the means of Ln-transformed pharmacokinetic parameters C_max, AUC_0-t and AUC_0-∞ were also calculated.
Results
Bioequivalence results for Ln-transformed test/reference ratios with 90% Confidence Intervals:

Penciclovir

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test</th>
<th>Reference</th>
<th>T/R ratio (%)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>5679.54</td>
<td>6285.64</td>
<td>90.36</td>
<td>80.50-101.42</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (ng.h/mL)</td>
<td>20212.70</td>
<td>21003.11</td>
<td>96.24</td>
<td>93.77-98.77</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (ng.h/mL)</td>
<td>21013.67</td>
<td>21775.53</td>
<td>96.50</td>
<td>94.02-99.05</td>
</tr>
</tbody>
</table>

Conclusion
The two-period, two-sequence, cross-over study design is appropriate. The study drug was administered after a supervised fast. A bioequivalence study under fasting conditions is acceptable.

Subject withdrawals and other protocol deviations were managed satisfactorily.

None of the pre-dose samples contained detectable level of penciclovir, length of the washout period was adequate. Blood collection time up to 12 hours post-dose was sufficient.

Analytical methods were satisfactory. The methods of statistical analysis used were appropriate. The 90% confidence intervals for the Ln-transformed AUC and C<sub>max</sub> for penciclovir lie within the acceptance criteria of 80-125%.

Based on the submitted bioequivalence study, the test and reference products, after a single dose (750 mg) administration, are considered to be bioequivalent.

Pharmacodynamics
The pharmacodynamic characteristics of famciclovir have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

Clinical efficacy and safety
No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of famciclovir.

Pharmacovigilance system
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.

Risk management plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.
**Expert report**
The clinical overview has been written by an appropriately qualified physician and is acceptable.

**Product literature**
All product literature (SmPC, PIL and labelling) is medically satisfactory.

**Clinical conclusion**
There are no objections to the approval the Marketing Authorisation applications for Famciclovir 125 mg, 250 mg and 500 mg Film-coated Tablets from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Famciclovir 125 mg, 250 mg and 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The use of famciclovir in the treatment of herpes simplex and herpes zoster virus infections is well established. Bioequivalence has been demonstrated between the proposed products and their reference product. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PILs are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new preclinical 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 ratio is, therefore, considered to be acceptable. Marketing Authorisations should be granted.