**Afamcivir 500 mg tablet, film-coated**

**06 July 2015, Versio 9/2.0**

**Public Summary of Risk Management Plan**

**(extract from the EU Safety Risk Management Plan)**

## 13.2 VI.2 Elements for a Public Summary

### 13.2.1 VI.2.1. Overview of disease epidemiology

Herpes simplex labialis, also known as cold sores, is a common condition usually caused by the herpes simplex virus, type 1 (HSV-1) (Pray, 2007). HSV-1 may infect children, but becomes more common with age; up to 80-90% of adult individuals in Europe and the United States (US) have antibodies to HSV-1 (Arduino & Porter, 2008; Looker & Garnett, 2005).

Not all those who are HSV-1 positive, however, develop cold sores. Large studies conducted in Europe and in the US have found that up to 20% of children <12 years of age and about 30-35% of adults have a history of cold sores (Löwaghen, 2002; Arduino & Porter, 2008). Recurrent episodes occur in about one third of patients (Opstelten et al., 2008).

### 13.2.2 VI.2.2. Summary of treatment benefits

#### 13.2.2.1 Current (gold) standards of treatment

The main treatment options of cold sores are antiviral medications administered topically (i.e. acyclovir or penciclovir cream) or orally (Opstelten et al., 2008; Harmenberg et al., 2010). In particular, acyclovir could be considered as the 'gold' standard for the treatment of cold sores because a cream preparation with this ingredient was the first topical antiviral treatment found on the market.

However, oral preparations are becoming increasingly popular because they may be more effective and afford shorter treatment durations (Hull et al., 2006). Valacyclovir, a prodrug of acyclovir, is approved as a 1-day oral treatment of cold sores. Clinical studies have demonstrated that oral valacyclovir (dosed 2'000 mg twice a day in one day) healed cold sore lesions one day faster than placebo (Spruance et al., 2006).

Following oral intake, famciclovir is converted into penciclovir, which is then activated against HSV-1 in cells infected with the virus. Importantly, penciclovir has a significantly longer intracellular duration than acyclovir (10 hours vs. <1 hour) and a 100-fold higher affinity for the viral enzyme (thymidine kinase) responsible for the molecule activation (Hull et al., 2006). These properties may translate into greater antiviral efficacy, as famciclovir therapy healed cold sore lesions two days faster than placebo (as opposed to one day faster in the valacyclovir study) (Spruance et al., 2006). However, head-to-head comparisons between famciclovir and valacyclovir have never been performed, and such difference in efficacy has not been conclusively established.

Oral famciclovir has been available for years under prescription for the treatment of herpes zoster (shingles), genital herpes and recurrent herpes labialis (cold sores) in patients with normal or compromised immune system. The recommended posology varies depending on the indication and status of the patient's immune system. The product is currently marketed in over 50 countries worldwide as a prescription only medicine. It has also been approved in New Zealand and Australia, and launched in New Zealand, as an OTC treatment of recurrent cold sores in adult patients with a healthy immune system.

#### 13.2.2.2 Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.)

Famciclovir 500 mg tablets, 3-tablets pack are indicated for subjects with normal immune systems (immunocompetent) in the treatment of recurrent cold sores, a very common skin disease worldwide. The infection usually occurs in childhood (primary infection) and often goes unnoticed (Harmenberg et al., 2010). The incidence of cold sores increases steadily with age, and up to 80-90% of adult individuals aged 50 years or older have antibodies to HSV-1 (Arduino & Porter, 2008; Looker & Garnett, 2005).

Cold sores are characterized by repeated attacks of vesicular eruptions on the lips and around the mouth mucosa. The frequency of attacks can vary from rare episodes to 12 or more attacks per year. Lesions require between 5-15 days to resolve (on average 7-8 days), depending on the immunocompetency of the affected person (Spruance et al., 1977; Grout & Barber, 1976; Spruance et al., 1977).

Although episodes of herpes labialis (cold sores) are generally non-serious and self-limiting in immunocompetent patients, many patients seek treatment due to discomfort, pain, disfigurement, and the infective nature of cold sores (Bader et al., 1978; Bader et al., 1978). For many sufferers the psychological consequences of cold sores can be of far greater concern and have a greater impact on their quality of life than the physical discomfort they experience (Schmid-Wendtner & Korting, 2004).

Subjects prone to cold sore outbreaks are typically concerned about the cosmetic impact of classical lesions that are defined as vesicles/pustules, ulcers/soft crusts, hard crusts (Augustin, 2001; Cunningham et al., 2012). Therefore, the time to resolution of classical lesion is highly clinically and psychologically relevant and has an important impact on the quality of life for the affected person (Esmann, 2001; Augustin, 2001; Arduino & Porter, 2008; Harmenberg et al., 2010).

### 13.2.2.3 A brief statement of the standard against which the medicine was judged: number of patients in pivotal studies and treatment regimes

A total of 984 patients aged 12-82 years were exposed to famciclovir in three company-sponsored studies of immunocompetent patients with recurrent herpes labialis (Studies 2403, RU02 and 2305).

Study 2403 compared two active treatment arms with placebo: 1500 mg once (single dose) and 750 mg twice a day for one day (single day) (Oeuvray et al., 2005; Spruance et al., 2006). The study was conducted at 28 centers in the United States, 10 centers in Canada, and three centers in Australia. A total of 701 adult patients aged at least 18 years received study medication, of whom 227 took famciclovir 1500 mg once, 220 took famciclovir 750 mg twice a day for one day and 254 received placebo.

Study RU02 was a single-arm study evaluating the effects of a single 1500 mg dose (500 mg tablets, 3-tablets pack) of famciclovir, taken within one hour of the onset of prodromal symptoms (i.e., tingling, itching, inflammation) (Kovganko, 2010). A total of 484 adult patients aged 18-79 years received at least one dose of study drug.

Study 2305 was a single-arm study evaluating the safety and pharmacokinetics of famciclovir in 12-17 year old adolescents with recurrent herpes labialis who were ≥40 kg body weight (Block et al., 2011). The clinic-initiated therapy consisted of a single 1500 mg dose (500 mg tablets, 3-tablets pack). A total of 53 patients were exposed to the study drug.

### 13.2.2.4 Results in lay language

An investigator-initiated trial published by Spruance and colleagues (Spruance et al., 1999), showed that famciclovir treatment (125, 250 or 500 mg three times a day for five days) afforded significant treatment benefit as compared to placebo. The median time to healing of cold sores was faster in the 500 mg famciclovir group than in the placebo group, both by investigator (four vs. six days, 33% reduction, p=0.010) and patient assessment (3.0 vs. 5.8 days, 48% reduction, p=0.008). The mean maximal lesion size was reduced in a dose-proportional manner, being 139, 105, 77, and 55 $mm^2$ for the placebo and 125, 250, and 500 mg famciclovir groups, respectively (p=0.040, linear regression). This study showed greater efficacy at the highest tested dose of famciclovir (3x500 mg daily). Drawing from these results, a total daily dose of 1500 mg was investigated in the following company-sponsored studies:

In Study 2403 (Oeuvray et al., 2005; Spruance et al., 2006), famciclovir 1500 mg once and 750 mg twice a day for one day were superior to placebo in reducing the time to healing of the primary lesion complex (4.4, 4.0 and 6.2 days, respectively, in the three study arms (p<0.001)), and that of all lesions (4.5, 4.1 and 6.6 days, respectively (p<0.001)). Furthermore, famciclovir 1500 mg once was superior to placebo in reducing the time to return to normal skin, the time to resolution of tenderness and pain (1.7 vs. 2.9 days, respectively; p<0.001), and the number of patients experiencing secondary lesions (11% vs. 18%, respectively).

In Study RU02, for all enrolled patients (n=480 adults), the mean time to healing from initiation of famciclovir therapy was estimated at 4.4 ± 2.1 days (Kovganko, 2010). Study 2305 included a small number of patients (n=53) and was primarily focused on evaluating the

safety and tolerability of a single 1500 mg dose of famciclovir in adolescents with cold sores (Block et al., 2011). Efficacy information gathered in this study is therefore limited. The majority of patients with active disease at baseline had symptoms (93.2%), of whom only four patients (9.1%) had symptoms at the end of the study.

#### 13.2.2.5 Post-authorization data which impacts on efficacy

There are no post-authorization data that impact on the efficacy of famciclovir 3x500 mg film-coated tablets.

### 13.2.3 VI.2.3. Unknowns relating to treatment benefits

There are insufficient efficacy data to support the use of famciclovir 3x500 mg film-coated tablets in children and adolescents <18 years of age. Therefore, the product is not indicated for use in this population. Furthermore, pregnant or breastfeeding women should not use famciclovir unless advised by their doctor.

No differences in efficacy were observed or are expected in terms of gender, age or race.

### 13.2.4 VI.2.4. Summary of safety concerns

**Table 13-3 Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Thrombocytopenia | Rarely, famciclovir may result in a decrease in the number of blood platelets.<br>Risk factors for this condition include bone marrow disorders, liver cirrhosis, and deficiency in folic acid or vitamin B12. | Patients with a previous history or symptoms of low blood platelets (unexplained bruising, reddish or purplish patches on the skin or nosebleeds), or with concurrent conditions that increase the risk of developing low blood platelets, should consult their doctor before using the product. |
| Abnormal liver function tests / Cholestatic jaundice | Increases in hepatic enzymes are a common adverse effect of famciclovir. These are usually asymptomatic and will resolve upon treatment discontinuation.<br>Rarely, famciclovir may be associated with cholestatic jaundice (symptoms include yellowing of the skin and/or eyes) | Patients with a previous history or symptoms of these disorders (such as yellowing of the skin and/or eyes) should consult their doctor before using the product. |
| Angioedema | Angioedema (i.e. swelling below the surface of the skin, including facial swelling, swelling around eye, eyelid swelling, throat swelling) is a rare adverse reaction to famciclovir.<br>Patients with symptoms of angioedema should stop taking famciclovir and seek medical help | Famciclovir is contraindicated in patients with a history of hypersensitivity to famciclovir, penciclovir or any of the ingredients. |

| Risk | What is known | Preventability |
|---|---|---|
| | immediately. This adverse reaction may resolve spontaneously or following treatment of the symptoms. | |
| Serious skin reactions | Serious allergic skin reactions may occur in isolated cases. Patients experiencing any symptoms (e.g. severe blistering of the skin or mucous membranes of the lips, eyes, mouth, nasal passages or genitals) should stop taking famciclovir and seek medical help immediately. | Famciclovir is contraindicated in patients with a history of hypersensitivity to famciclovir, penciclovir or any of the ingredients. |
| Hallucinations | Hallucinations (seeing or hearing things that are not really there) have occurred rarely in patients taking famciclovir. | Patients at risk of hallucinations (e.g. with a history of psychiatric disorders, dementia or seizures) should be referred to their doctor for guidance. |

**Table 13-4 Important potential risks**

| Risk | What is known |
|---|---|
| Use in patients with renal impairment | Dose adjustments are necessary in patients with kidney impairment because of the reduced drug elimination rate. Failing to adjust the dosage may result in overdose and possible aggravation of kidney problems.<br>Patients with kidney conditions should consult their doctor before taking famciclovir so they can receive guidance on the appropriate dose.<br>Pharmacists must refer patients with kidney conditions to their doctor for guidance. |
| Use in patients with hepatic impairment | Following oral intake, famciclovir is converted into the agent penciclovir, which is active against the herpes virus. As the liver plays an important role in this pathway, famciclovir may be less effective in patients with liver dysfunction.<br>All patients with liver conditions should consult their doctor for guidance before taking famciclovir. |
| Increased virus resistance | The wide spread use of famciclovir may result in mutations that enhance viral resistance to the product. Although this risk cannot be excluded, the long experience accumulated with various antiviral agents has shown a remote risk of viral resistance in patients with a healthy immune system. |
| Use in lactose intolerant patients | Each tablet of famciclovir contains 107.4 mg of lactose.<br>Patients with intolerance to sugars, including lactose, should consult their doctor for guidance before taking famciclovir. |
| Off-label use (including paediatric patients) | Famciclovir is available over-the-counter (without prescription) only for the treatment of recurrent herpes labialis (cold sores) in adult patients with a healthy immune system.<br>All other patients, including children and adolescents <18 |

| Risk | What is known |
|---|---|
| | years of age, should consult their doctor for guidance. |
| Convulsion | The risk of seizures is under close monitoring, but to date there is no evidence that the use of famciclovir may cause seizures. |

**Table 13-5 Missing information**

| Risk | What is known |
|---|---|
| Use during pregnancy or lactation | Due to the lack of adequate data, famciclovir is not to be used during pregnancy or breast-feeding unless clearly necessary.<br>Pregnant or breastfeeding women should consult their doctor for guidance before using famciclovir. |

## 13.3 VI.2.5 Summary of risk minimization measures by safety concern

These additional risk minimization measures are for the following risks:

- Thrombocytopenia (low blood platelet count)
- Abnormal liver function tests / Cholestatic jaundice (Increased blood levels of liver enzymes / yellow colour of the skin and whites of the eyes)
- Angioedema (swelling under the skin)
- Serious skin reactions (Severe blistering of the skin or mucous membranes)
- Hallucinations
- Use in patients with renal impairment
- Use in patients with hepatic (liver) impairment
- Use in lactose intolerant patients
- Off-label use, including paediatric patients (use in unapproved indications)
- Use during pregnancy or lactation

**Table 13-6 Summary of risk minimization measures**

| Risk minimization measure(s) |
|---|
| **Objective and rationale**<br>Additional risk minimization measures have been put in place to alert Doctors and Pharmacists that famciclovir is available in pharmacies without prescription, and make them aware of important safety information regarding this product.<br>Pharmacists will ask questions about the patients' medical history and will refer to the doctor for consultation those who have signs of any of the above conditions.<br><br>**Main risk minimisation measures**<br>Direct HCP communication prior to launch: |

| Risk minimization measure(s) |
| --- |
| – Dear Doctor letter<br>– Dear Pharmacist letter<br>– Questionnaire (to be completed in person/via telephone or distributed online/by tracked-mail response) to assess and track pharmacists' comprehension of product reference safety information and "Dear Pharmacist" letter |

## 13.4 VI.2.6 Planned post authorization development plan

### 13.4.1 List of studies in post authorization development plan

A planned post-authorization development plan is not required for this product.

### 13.4.2 Studies which are a condition of the marketing authorization

No studies have been established as conditions of the marketing authorization.

## 13.5 VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable as this is the first RMP for famciclovir 3x500 mg film-coated tablets.