Core Safety Profile

Active substance: Zavirlukast
Pharmaceutical form(s)/strength: Tablets, 20mg
P-RMS: IE/H/PSUR/0030/001
Date of FAR: 13.09.2010
4.2 Posology and method of administration

**Elderly**

The clearance of the product is reduced in elderly patients (>65 years old), such that Cmax and AUC are approximately twice those of younger adults. However, accumulation of the product is not evident in elderly patients. In clinical trials, elderly patients receiving a dose of 20 mg twice daily were not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events. Therapy may be initiated at 20 mg twice daily and adjusted according to clinical response.

**Children**

The safety and efficacy of the product in children under 12 years has not been established. Until further information on use in children is available, the product is not recommended in this age group.

**Renal impairment**

Experience is limited in patients with mild to severe renal impairment, so clear dose recommendations cannot be given. Therefore, the product should be used with caution in these patients.

4.3 Contraindications

The product should not be given to patients who have previously experienced hypersensitivity to the product or any of its ingredients.

The product is contraindicated for patients with hepatic impairment including hepatic cirrhosis.

4.4 Special warnings and special precautions for use

The product should be taken regularly to achieve benefit, even during symptom free periods. Zavirlukast therapy should normally be continued during acute exacerbations of asthma.

As with inhaled steroids and cromones (disodium cromoglycate, nedocromil sodium), the product is not indicated for use in the reversal of bronchospasm in acute asthma attacks.

The product has not been evaluated in the treatment of labile (brittle) or unstable asthma. Inhaled and oral corticosteroids should not be stopped abruptly after initiation of the product.

Rarely, patients with asthma on anti-leukotriene medications, including the product, may present with systemic eosinophilia, eosinophilic pneumonia or with clinical features of systemic vasculitis, consistent with Churg-Strauss syndrome. Presentations may involve various body systems including vasculitic rash, worsening pulmonary symptoms, cardiac complications or neuropathy. These events have usually, but not always, been associated with reductions and/or withdrawal of steroid therapy. The possibility that leukotriene receptor antagonists, including the product, may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. If a patient develops an eosinophilic conditions, or a Churg-Strauss Syndrome type illness, the product should be stopped. A rechallenge test should not be performed and treatment should not be restarted.
Elevations in serum transaminases can occur during treatment with the product. These are usually asymptomatic and transient but could represent early evidence of hepatotoxicity, and have very rarely been associated with more severe hepatocellular injury, fulminant hepatitis and liver failure, some of which resulted in a fatal outcome. Extremely rarely, cases of fulminant hepatitis and liver failure have been reported in patients in whom no previous clinical signs or symptoms of liver dysfunction were reported (see also section 4.8).

If clinical symptoms or signs suggestive of liver dysfunction occur (e.g. anorexia, nausea, vomiting, right upper quadrant pain, fatigue, lethargy, flu-like symptoms, enlarged liver, pruritus and jaundice), the product should be discontinued. The serum transaminases, in particular serum ALT, should be measured immediately, and the patient managed accordingly. Physicians may consider the value of liver function testing. Periodic serum transaminase testing has not proven to prevent serious injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug may enhance the likelihood for recovery. Patients in whom the product was withdrawn because of hepatotoxicity with no other attributable cause should not be reexposed to the product.

The product 20 mg contains 45 mg lactose monohydrate in each tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucosegalactose malabsorption, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The product may be administered with other therapies routinely used in the management of asthma and allergy. Inhaled steroids, inhaled and oral bronchodilator therapy, antibiotics and antihistamines are examples of agents which have been co-administered with the product without adverse interaction.

The product may be administered with oral contraceptives without adverse interaction.

Co-administration with acetylsalicylic acid (aspirin) may result in increased plasma levels of zavirlukast, by approximately 45%. It is unlikely that such an increase will be associated with clinically relevant effects.

Co-administration with erythromycin will result in decreased plasma levels of zavirlukast, by approximately 40%.

In clinical trials co-administration with theophylline resulted in decreased levels of the product, by approximately 30%, but with no effect on plasma theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered zavirlukast.

Co-administration with terfenadine resulted in a 54% decrease in AUC for the product, but with no effect on plasma terfenadine levels.

Co-administration with warfarin results in an increase in maximum prothrombin time by approximately 35%. It is therefore recommended that if the product is co-administered with warfarin, prothrombin time should be closely monitored. The interaction is probably due to an inhibition by the product of the cytochrome P450 2C9 isoenzyme system.

4.6 Pregnancy and lactation

In animal studies, zavirlukast did not have any apparent effect on fertility and did not appear to have any teratogenic or selective toxic effect on the foetus. However, the safety of zavirlukast in human pregnancy has not been established. The potential risks should be
weighed against the benefits of continuing therapy during pregnancy and the product should be used during pregnancy only if clearly needed.
The product is excreted in human breast milk. The product should not be administered to mothers who are breast-feeding.

4.7 Effects on ability to drive and use machines
There is no evidence that the product affects the ability to drive and use machinery.

4.8 Undesirable effects
Administration of the product may be associated with the following undesirable effects. The reactions are classified according to frequency (very common $\geq 1/10$, common $\geq 1/100$ to $<1/10$; uncommon $\geq 1/1000$ to $<1/100$; rare $\geq 1/10000$ to $<1/1000$; very rare $<1/10000$).

Infections and infestations
Very common: Infection

Blood and the lymphatic system disorders
Very rare: Agranulocytosis$^{1,2}$
Rare: Bleeding disorders$^1$

Immune system disorders
Uncommon: Hypersensitivity$^1$
Rare: Angioedema$^1$.

Psychiatric disorder
Uncommon: Insomnia$^1$

Nervous system disorder
Common: Headache

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain

Hepatobiliary disorders
Common: Elevations in transaminase levels
Uncommon: Hyperbilirubinemia
Rare: Hepatitis
Very rare: Fulminant hepatitis\textsuperscript{2}, hepatic failure\textsuperscript{2}

**Skin and subcutaneous disorder**
Common: Rash\textsuperscript{1}
Uncommon: Urticaria\textsuperscript{1}, pruritus\textsuperscript{1}.
Rare: Blister\textsuperscript{1}

**Musculoskeletal and connective tissue disorder**
Common: Myalgia
Uncommon: Arthralgia

**General disorders and administration site conditions**
Uncommon: Oedema\textsuperscript{1}, malaise\textsuperscript{1}

**Injury, Poisoning and Procedural Complications**
Rare: Bruising\textsuperscript{1}

\textsuperscript{1} These events have usually resolved following cessation of therapy.
\textsuperscript{2} Frequency is based on post-marketing data.

**Hepatic Effects**
Elevated serum transaminase levels have been observed in clinical trials with zavirlukast. The changes usually resolved during continued treatment or following cessation of therapy. Rarely the transaminase profile has been consistent with a drug-induced hepatitis, which resolved following cessation of zavirlukast therapy.

Hyperbilirubinemia without elevated liver function tests has also been associated with the use of the product.

During post-marketing experience there have been rare reports of symptomatic hepatitis, with and without hyperbilirubinemia, associated with the use of the product. These cases have usually resolved following cessation of therapy with the product. The predominate majority of cases have been reported in females (see also section 4.4).

**Infection**
In placebo-controlled clinical trials, an increased incidence of infection has been observed in elderly patients given the product. Infections were usually mild, predominantly affecting the respiratory tract and not necessitating withdrawal from therapy with zavirlukast.
4.9 Overdose

Reports of overdose with zavirlukast have been received. In reports with excessive zavirlukast doses no significant symptoms have been observed.

Gastric lavage and/or an installation of charcoal may be considered in selected cases of the excessive overdose of zavirlukast. Management should be supportive.