Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Accolate 20mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Accolate contains 20mg of zafirlukast in each tablet.

Excipients: Lactose.
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet
Product imported from the UK:
White, round, biconvex film-coated tablets intagliated with ‘Accolate 20’ on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Accolate is indicated for the prophylaxis and chronic treatment of asthma.

4.2 Posology and method of administration

Accolate is taken to prevent asthma attacks and should therefore be taken continuously.

Adults and Children aged 12 years and over:
Therapy should be initiated at 20mg twice daily. The usual maintenance dosage is 20mg twice daily. Increasing the dose, titrating to a maximum of 40mg twice daily, may provide additional benefit. This dose should not be exceeded because higher doses may be associated with hepatotoxicity.

As food may reduce the bioavailability of zafirlukast, Accolate should not be taken with meals.

Elderly
The clearance of zafirlukast is reduced in elderly patients >65 years old), such that Cmax and AUC are approximately twice those of younger adults. However, accumulation of Accolate is not evident in elderly patients. In clinical trials, elderly patients receiving a dose of 20mg 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 20mg twice daily and adjusted according to clinical response.

Children:
The safety and efficacy of Accolate in children under 12 years has not been established. Until further information on use in children is available, Accolate 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, Accolate should be used with caution in these patients.

4.3 Contraindications

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

ingredients.

Accolate is contraindicated for patients with hepatic impairment including hepatic cirrhosis.

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

4.4 Special warnings and precautions for use

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

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

Accolate 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 Accolate.

Rarely, patients with asthma on anti-leukotriene medications, including Accolate, 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 in oral steroid therapy. The possibility that leukotriene receptor antagonists, including Accolate, may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. If a patient develops an eosinophilic condition, or a Churg-Strauss syndrome type illness, Accolate 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 Accolate.

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 whom no previous clinical signs or symptoms suggestive 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, pruritis and jaundice), Accolate 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 ACCOLATE was withdrawn because of hepatotoxicity with no other attributable cause should not be re-exposed to ACCOLATE.

Accolate 20 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Accolate 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 Accolate without adverse interaction.

Accolate may be administered with oral contraceptives without adverse interaction.

Co-administration with acetylsalicylic acid (“aspirin”) may result in increased plasma levels of zafirlukast, 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 zafirlukast, by approximately 40%.

In clinical trials co-administration with theophylline resulted in decreased levels of zafirlukast, 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 Accolate.

Co-administration with terfenadine resulted in a 54% decrease in AUC for zafirlukast, 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 Accolate is co-administered with warfarin, prothrombin time should be closely monitored. The interaction is probably due to an inhibition by zafirlukast of the cytochrome P450 2C9 isoenzyme system.

4.6 Fertility, pregnancy and lactation

In animal studies, zafirlukast 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 Accolate in human pregnancy has not been established. The potential risks should be weighed against the benefits of continuing therapy during pregnancy and Accolate should be used during pregnancy only if clearly needed.

Zafirlukast is excreted in human breast milk. Zafirlukast 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 Accolate affects the ability to drive and use machinery.

4.8 Undesirable effects

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

Infections and infestations:
Very common: Infection

Blood and the lymphatic system disorders
Rare: Bleeding disorders[1]
Very rare: Agranulocytosis[1,2]

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[2],,hepatic failure[2]

Skin and subcutaneous disorder:
Common: Rash[1]
Uncommon: Urticaria1, pruritus[1].
Rare: Blister[1]

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

General disorders and administration site conditions:
Uncommon: Oedema[1], malaise[1]

Injury, Poisoning and Procedural Complications:
Rare: Bruising[1]

[1]These events have usually resolved following cessation of therapy.
[2]Frequency is based on post-marketing data.

Hepatic Effects: Elevated serum transaminase levels have been observed in clinical trials with Accolate. 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 Accolate therapy.

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

During post-marketing experience there have been rare reports of symptomatic hepatitis, with and without hyperbilirubinemia, associated with the use of Accolate. These cases have usually resolved following cessation of therapy with Accolate. 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 Accolate. Infections were usually mild, predominantly affecting the respiratory tract and not necessitating withdrawal from therapy with Accolate.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The ATC Code is RO3DC

Leukotriene (LT) production and receptor occupation has been implicated in the pathophysiology of asthma. Effects

include smooth muscle contraction, airway oedema and altered cell activity associated with the inflammatory process including eosinophil influx to the lung. These effects contribute to and correlate with the signs and symptoms of asthma. Accolate acts as an anti-inflammatory agent, reducing the effect of these pro-inflammatory mediators.

Accolate is a highly selective and potent oral peptide competitive antagonist of LTC4, LTD4, and LTE4, components of slow reacting substance of anaphylaxis. In vitro studies have shown that Accolate antagonises the contractile activity of all three peptide leukotrienes (leukotriene C4, D4, and E4) in human conducting airway smooth muscle to the same extent. Animal studies have shown Accolate to be effective in preventing peptide leukotriene-induced increases in vascular permeability, which gives rise to oedema in the airways, and to inhibit peptide leukotriene-induced influx of eosinophils into the airways.

The specificity of Accolate has been shown in clinical studies, by its action on leukotriene receptors and not prostaglandin, thromboxane, cholinergic and histamine receptors.

In clinical trials, Accolate has been shown to have anti-inflammatory properties. Dosing with Accolate for five days reduced cellular and non-cellular components of inflammation in the airway induced by antigen challenge. In a placebo-controlled study where segmental bronchoprovocation with allergen was followed by bronchoalveolar lavage 48 hours later, zafirlukast decreased the rise in basophils, lymphocytes and histamine, and reduced the stimulated production of superoxide by alveolar macrophages. Accolate attenuated the increase in bronchial hyper responsiveness that follows inhaled allergen challenge and the bronchoconstriction induced by platelet activating factor.

Further, methacholine sensitivity was diminished by long-term dosing with Accolate 20mg twice daily. Further, in clinical trials evaluating chronic therapy with Accolate the lung function measured when plasma levels were at trough showed improvements over baseline that were consistent with a sustained decrease in obstruction due to inflammatory components.

Accolate shows a dose dependent inhibition of bronchoconstriction induced by inhaled leukotriene D4. Asthmatic patients are approximately 10-fold more sensitive to the bronchoconstricting activity of inhaled leukotriene D4. A single oral dose of Accolate can enable an asthmatic patient to inhale 100 times more leukotriene D4 and shows significant protection at 12 and 24 hours.

Accolate inhibits the bronchoconstriction caused by several kinds of challenge, such as the response to sulphur dioxide, exercise and cold air. Accolate attenuates the early and late phase inflammatory reaction caused by various antigens such as grass, cat dander, ragweed and mixed antigens. In some patients, Accolate completely prevents the onset of asthma attacks induced by exercise and allergens.

In asthmatic patients not adequately controlled by beta-agonist therapy (given as required), Accolate is indicated as first line maintenance therapy. In symptomatic patients Accolate improves symptoms (reducing daytime and nocturnal asthmatic symptoms), improves lung function, reduces the need for concomitant beta-agonist medication and reduces incidence of exacerbations. Similar benefits have been seen in patients with more severe asthma receiving high dose inhaled steroids.

In clinical studies, there was a significant first-dose effect on baseline bronchomotor tone observed within 2 hours of dosing, when peak plasma concentrations had not yet been achieved. Initial improvements in asthma symptoms occurred within the first week and often within the first few days of treatment with Accolate.

Accolate is administered as a twice-daily oral therapy and may, therefore, be of particular value in patients who may experience compliance or administration difficulties with inhaled maintenance therapy.

5.2 Pharmacokinetic properties

Peak plasma concentrations of zafirlukast are achieved approximately 3 hours after oral administration of Accolate.

Following twice-daily administration of Accolate (30-80mg bd), accumulation of zafirlukast in plasma was low (not detectable - 2.9 times first dose values; mean 1.45; median 1.27). The terminal half-life of zafirlukast is approximately 10 hours. Steady state plasma concentrations of zafirlukast were proportional to the dose and predictable from single-

dose pharmacokinetic data.

Pharmacokinetics of zafirlukast in adolescents and adults with asthma were similar tothose of healthy adult males. When adjusted for body weight, the pharmacokinetics of zafirlukast are not significantly different between men and women.

Administration of Accolate with food increased the variability in the bioavailability of zafirlukast and reduced bioavailability in most (75%) subjects. The net reduction was approximately 40%.

Following a radiolabelled dose of zafirlukast approximately 10% of the radioactivity was recovered in the urine and 89% was recovered in the faeces. Zafirlukast is extensively metabolised. Four metabolites account for the 10% of dose recovered in urine, zafirlukast itself is not found in urine. In addition to zafirlukast, three of these metabolites have been identified in human plasma and in a standard in-vitro test of activity were found to be at least 90-fold less potent than zafirlukast.

Elderly subjects and subjects with stable alcoholic cirrhosis demonstrated an approximately two fold increase in Cmax and AUC compared to normal subjects given the same doses of Accolate.

There are no significant differences in the pharmacokinetics of zafirlukast in renally impaired patients and normal subjects.

Zafirlukast is approximately 99% protein bound to human plasma proteins, predominantly albumin, over the concentration range 0.25-4.0 microgram/ml.

5.3 Preclinical safety data

After multiple doses of greater than 40mg/kg/day for up to 12 months, liver enlargement associated with degenerative/fatty change or glycogen deposition was seen in rats, mice and dogs. Histiocytic aggregates were seen in a number of tissues of dogs.

Male mice given 300mg/kg zafirlukast daily had an increased incidence of hepatocellular adenomas compared to control animals. Rats given 2000 mg/kg zafirlukast daily had an increased incidence of urinary bladder papilloma compared to control animals. Zafirlukast was not mutagenic in a range of tests. The clinical significance of these findings during the long term use of Accolate in man is unknown.

In animal studies, zafirlukast did not have any effect on the offspring of female rats that received the drug during lactation, but neonatal/juvenile rats and dogs were particularly sensitive to the adverse effects of zafirlukast, including fat necrosis. The relevance of these findings to humans is unknown. Zafirlukast should not be administered to mothers who are breast feeding.

There were no other notable findings from the preclinical testing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Lactose monohydrate
Microcrystalline cellulose
Povidone
Magnesium stearate

Film-coating:
Hypromellose
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Carton containing 56 tablets in aluminium laminate/foil blister packs.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/198/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th June 2007

Date of last renewal: 8th June 2012

10 DATE OF REVISION OF THE TEXT

August 2013