COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Montelukast Glenmark 10 mg film-coated tablets (montelukast sodium)

## NL/H/4524/001/DC

## Date: 24 February 2023

**This module reflects the scientific discussion for the approval of Montelukast Glenmark 10 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/2273/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.**

Safeguarding public health

MHRA

# Public Assessment Report

# Decentralised Procedure

## MONTELUKAST 10 MG FILM-COATED TABLETS

(Montelukast sodium)

**Procedure No: UK/H/2273/001/DC**

**UK Licence No: PL 25258/0010**

**GLENMARK GENERICS (EUROPE) LIMITED**

# LAY SUMMARY

On 15 December 2011, Germany, the Netherlandsand the UK agreed to grant a Marketing Authorisation to Glenmark Generics (Europe) Limited for the medicinal product Montelukast 10 mg Film-coated Tablets (PL 25258/0010; UK/H/2273/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 23 February 2012.

Montelukast 10 mg Film-coated Tablets is a Prescription Only Medicine (POM) used for:

- the treatment of asthma in patients who are not adequately controlled on their medication and need additional therapy
- those asthmatic patients in whom montelukast is indicated in asthma to provide symptomatic relief of seasonal allergic rhinitis.
- prevention of the narrowing of airways triggered by exercise.

Montelukast is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in the lungs. By blocking leukotrienes, montelukast improves asthma symptoms, helps control asthma and improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Montelukast 10 mg Film-coated Tablets outweigh the risks.

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# Module 1

| | |
|---|---|
| **Product Name** | Montelukast 10 mg Film-coated Tablets |
| **Type of Application** | Generic, Article 10(1) |
| **Active Substances** | Montelukast sodium |
| **Form** | Film-coated tablet |
| **Strength** | 10 mg |
| **MA Holder** | Glenmark Generics (Europe) Limited,<br>Laxmi House, 2-B Draycott Avenue, Kenton, Harrow,<br>Middlesex, HA3 0BU, UK. |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Germany and the Netherlands |
| **Procedure Number** | UK/H/2273/001/DC |
| **Timetable** | Day 210 –15 December 2011 |

# Module 2
# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT
Montelukast 10 mg Film-coated Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg montelukast.
Excipient: Lactose monohydrate 89.3 mg per tablet.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM
Film-coated tablet

Beige, round, 8 mm biconvex, film-coated tablets, engraved with 'G' on one side and '392' on other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications
Montelukast is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting beta-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

### 4.2 Posology and method of administration
The dosage for adults 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10-mg tablet daily to be taken in the evening.

*Method of administration:*
For oral use.
The tablet should be swallowed with a sufficient amount of water.

*General recommendations*
The therapeutic effect of Montelukast on parameters of asthma control occurs within one day. Montelukast may be taken with or without food. Patients should be advised to continue taking Montelukast even if their asthma is under control, as well as during periods of worsening asthma.

Montelukast should not be used concomitantly with other products containing the same active ingredient, montelukast.

No dosage adjustment is necessary for the elderly, or for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.
Montelukast 5 mg Chewable Tablets are available for paediatric patients 6 to 14 years of age.
Montelukast 4 mg Chewable Tablets are available for paediatric patients 2 to 5 years of age.

*Therapy with Montelukast in relation to other treatments for asthma*
Montelukast can be added to a patient's existing treatment regimen.

*Inhaled corticosteroids*
Treatment with Montelukast can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting β-agonists provide inadequate clinical control. Montelukast should not be substituted for inhaled corticosteroids (see section 4.4).

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

**4.4 Special warnings and precautions for use**

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be substituted for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy (see section 4.8). These cases usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

This medicinal product contains lactose (monohydrate*)*.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

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

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

*In vitro* studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of drugs metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

**4.6 Fertility, pregnancy and lactation**

*Used during pregnancy*
Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonic/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between Montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast should not be used during pregnancy unless clearly necessary.

*Use during lactation*
Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known if montelukast is excreted in human milk.

Montelukast should not be used during lactation unless clearly necessary

**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, in very rare cases, individuals have reported drowsiness or dizziness (see section 4.8)

**4.8 Undesirable effects**

Montelukast has been evaluated in clinical studies as follows:

- 10-mg film-coated tablets in approximately 4000 adult asthmatic patients 15 years of age and older.
- 10-mg film-coated tablets in approximately 400 adult asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
- 5-mg chewable tablets in approximately 1750 paediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100, ≤1/10) in asthmatic patients treated with montelukast and at a greater incidence than in patients treated with placebo:

| Body System Class | Adult Patients 15 years and older (two 12-week studies; n=795) | Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615) |
|---|---|---|
| Nervous system disorders | headache | headache |
| Gastro-intestinal disorders | abdominal pain | |

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

*Post marketing Experience*

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.

| **System Organ Class** | **Adverse Experience Term** | **Frequency Category*** |
|---|---|---|
| Infections and infestations | upper respiratory infection† | Very Common |
| Blood and lymphatic system disorders | increased bleeding tendency | Rare |
| Immune system disorder | hypersensitivity reactions including anaphylaxis | Uncommon |
| | hepatic eosinophilic infiltration | Very Rare |
| Psychiatric disorders | dream abnormalities including nightmares, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression | Uncommon |
| | tremor | Rare |
| | hallucinations, suicidal thinking and behaviour (suicidality) | Very Rare |
| Nervous system disorder | dizziness, drowsiness paraesthesia/hypoesthesia, seizure | Uncommon |
| Cardiac disorders | palpitations | Rare |
| Respiratory, thoracic and mediastinal | epistaxis | Uncommon |
| | Churg-Strauss Syndrome (CSS) (see section 4.4) | Very Rare |

| | | |
|---|---|---|
| disorders | | |
| Gastrointestinal disorders | diarrhoea‡, nausea‡, vomiting‡ | Common |
| | dry mouth, dyspepsia | Uncommon |
| Hepatobiliary disorders | elevated levels of serum transaminases (ALT, AST) | Common |
| | hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury). | Very Rare |
| Skin and subcutaneous tissue disorders | rash‡ | Common |
| | bruising, urticaria, pruritus | Uncommon |
| | angiooedema | Rare |
| | erythema nodosum | Very Rare |
| Musculoskeletal, connective tissue and bone disorders | arthralgia, myalgia including muscle cramps | Uncommon |
| General disorders and administration site conditions | pyrexia‡ | Common |
| | asthenia/fatigue, malaise, oedema, | Uncommon |

**Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).*

*†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.*

*‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.*

## 4.9 Overdose

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdosee reports.

*Symptoms:*

The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

*Treatment:*

It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** , Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonist

ATC-code: R03D C03

The cysteinyl leukotrienes ($LTC_4$, $LTD_4$, $LTE_4$) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated

effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled $LTD_4$ at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a beta-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning $FEV_1$ (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total beta-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclometasone plus montelukast vs beclometasone, respectively for $FEV_1$: 5.43% vs 1.04%; beta -agonist use: -8.70% vs 2.64%). Compared with inhaled beclometasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclometasone provided a greater average treatment effect (% change from baseline for montelukast vs beclometasone, respectively for $FEV_1$: 7.49% vs 13.3%; beta --agonist use: -28.28% vs -43.89%). However, compared with beclometasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclometasone achieved an improvement in $FEV_1$ of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10-mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Night time Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function ($FEV_1$ 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" beta-agonist use (-11.7% vs +8.2% change from baseline).

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in $FEV_1$ 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline $FEV_1$ 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients (maximal fall in $FEV_1$ 18.27% vs 26.11%; time to recovery to within 5% of baseline $FEV_1$ 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control ($FEV_1$ 8.55% vs -1.74% change from baseline and decrease in total beta-agonist use -27.78% vs 2.09% change from baseline).

## 5.2 Pharmacokinetic properties

*Absorption.* Montelukast is rapidly absorbed following oral administration. For the 10-mg film-coated tablet, the mean peak plasma concentration ($C_{max}$) is achieved 3 hours ($T_{max}$) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and $C_{max}$ are

not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10-mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5-mg chewable tablet, the $C_{max}$ is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

*Distribution.* Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 litres. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

*Biotransformation.* Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

*In vitro* studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

*Elimination.* The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

*Characteristics in patients.* No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).
With high doses of montelukast (20- and 60-fold the recommended adult dose), decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

## 5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose).

In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m$^2$ and 30,000 mg/m$^2$ in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold based on systemic exposure).

Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Core:
Cellulose microcrystalline
Lactose monohydrate
Croscarmellose sodium
Hydroxypropylcellulose (E463)
Magnesium stearate

Film coating:
Hypromellose (E464)
Hydroxypropylcellulose (E463)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Carnauba wax (E903)
Iron oxide red (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months
30 days after first opening

### 6.4 Special precautions for storage

Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions. Use within 30 days of opening.

### 6.5 Nature and contents of container

HDPE containers with polypropylene child resistant closures, also contains a canister of silica gel desiccant with a cardboard carton.
Pack sizes: 20, 28, 30

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Limited
Laxmi House, 2-B Draycott Avenue,
Kenton, Harrow, Middlesex, HA3 0BU,
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0010

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2012

## 10 DATE OF REVISION OF THE TEXT

23/02/2012

# Module 3

**The leaflet text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder is required to submit the leaflet mock-up to the relevant regulatory authorities for approval before marketing the product in a particular member state.**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

Montelukast 10 mg Film-coated Tablets

montelukast

**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 any further questions, 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.

**In this leaflet**:


### 1. WHAT MONTELUKAST 10 MG FILM-COATED TABLETS ARE AND WHAT IT IS USED FOR

Montelukast 10 mg Film-coated Tablets is a Leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs and also cause allergy symptoms. By blocking Leukotrienes, Montelukast 10 mg Film-coated Tablets improves and controls the symptoms of asthma and improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

Your doctor has prescribed Montelukast 10 mg Film-coated Tablets to treat asthma, preventing your asthma symptoms during the day and night.
- Montelukast 10 mg Film-coated Tablets is used for the treatment of patients who are not adequately controlled on their medication and need additional therapy.
- Montelukast 10 mg Film-coated Tablets also helps prevent the narrowing of airways triggered by exercise.
- In those asthmatic patients in whom Montelukast 10 mg Film-coated Tablets is indicated in asthma, Montelukast 10 mg Film-coated Tablets can also provide relief of seasonal allergic rhinitis.

What is asthma?

Asthma is a long-term disease. Asthma includes:
- Difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.

- Sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
- Swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: Coughing, wheezing, and chest tightness.

What are seasonal allergies?

Seasonal allergies (also known as hay fever or season allergic rhinitis) are known as allergic response often caused by airborne pollen from trees, grass and weeds. The symptopms of seasonal allergic may include stuffy, runny and/or itchy nose; sneezing; watery, swollen, red, itchy eyes.

## 2. BEFORE YOU TAKE MONTELUKAST 10 MG FILM-COATED TABLETS

Tell your doctor about any medical problems or allergies you have now or have had.

**Do not take Montelukast 10 mg Film-coated Tablets**
- if you are allergic (hypersensitive) to montelukast or any of the other ingredients of Montelukast 10 mg Film-coated Tablets

**Take special care with Montelukast 10 mg Film-coated Tablets**
- If your asthma or breathing gets worse, tell your doctor immediately.
- Oral Montelukast 10 mg Film-coated Tablets is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you. Always have your inhaled rescue medicine for asthma attacks with you.
- Any patient on anti-asthma medicines should be aware that if you develop a combination of symptoms such as a flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash, you should consult your doctor.
- You should not take aspirin or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDS) if they make your asthma worse.
- It is important that you or your child take all asthma medications prescribed by your doctor. Montelukast should not be substituted for other asthma medications your doctor has prescribed for you.

*Use in children*
For children 2 to 5 years old, Montelukast 4 mg Chewable Tablets are available.
For children 6 to 14 years old, Montelukast 5 mg Chewable Tablets are available.

**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. This includes medicines, herbal remedies, health products or supplements that you have obtained without a prescription.

Treatment with Montelukast 10 mg Film-coated Tablets can be affected by other medicines. Some medicines may affect how montelukast works, or montelukast may affect how other medicines work.Tell your doctor if you are taking any of the following medicines as special care may be required:
- Phenobarbital (used for treatment of epilepsy)
- Phenytoin (used for treatment of epilepsy)
- Rifampicin (used to treat tuberculosis and other infections)

**Taking Montelukast 10 mg Film-coated Tablets with food and drink**
Montelukast 10 mg Film-coated Tablets may be taken with or without food.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

*Pregnancy*
Women who are pregnant or intend to become pregnant should consult their doctor before taking Montelukast 10 mg Film-coated Tablets. Your doctor will assess whether you can take Montelukast 10 mg Film-coated Tablets during this time.

*Lactation*
It is not known if Montelukast 10 mg Film-coated Tablets appears in breast milk. You should consult your doctor before taking Montelukast 10 mg Film-coated Tablets if you are breast feeding or if you are planning to breast feed.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed

Montelukast 10 mg Film-coated Tablets is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with Montelukast 10 mg Film-coated Tablets may affect some patients ability to drive or operate machinary, therefore caution is advised.

**Important information about some of the ingredients of Montelukast 10 mg Film-coated Tablets**
Montelukast 10 mg Film-coated Tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars (rare hereditary problems, galactose intolerance, the lapp lactose deficiency of glucose-galactose malabsorption), you should contact your doctor before taking this medicine.

## 3. HOW TO TAKE MONTELUKAST 10 MG FILM-COATED TABLETS

Always take Montelukast 10 mg Film-coated Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Take Montelukast 10 mg Film-coated Tablets by mouth only.
- You should take only one tablet of Montelukast 10 mg Film-coated Tablets once a day as prescribed by your doctor.
- It should be taken even when you have no symptoms or have an actute asthma attack.
- Always take Montelukast 10 mg Film-coated Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

<u>For adults 15 years of age and older</u>
One 10 mg tablet to be taken daily in the evening. Montelukast 10 mg Film-coated Tablets may be taken with or without food.

If you are taking Montelukast 10 mg Film-coated Tablets, be sure that you do not take any other products that contain the same active ingredient, montelukast.

**If you take more Montelukast 10 mg Film-coated Tablets than you should**
If you take more Montelukast 10 mg Film-coated Tablets than you should contact your doctor or pharmacist immediately.

There were no side effects reported in the majority of over-dosage reports. The most frequently occuring effects reported with overdosage in adults and children included abdominal pain, sleepiness, thirst, headache, vomitting and hyperactivity (unusally active).

**If you forget to take Montelukast 10 mg Film-coated Tablets**
Take your tablet as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Montelukast 10 mg Film-coated Tablets**
Montelukast 10 mg Film-coated Tablets can treat your asthma only if you continue to take it. It is important to continue taking Montelukast 10 mg Film-coated Tablets for as long as your doctor prescribes. It will help control your asthma.

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

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Montelukast 10 mg Film-coated Tablets can cause side effects, although not everybody gets them.

In clinical studies the most commonly (in more than 1 in 100, or less than 1 in 10 treated patients) reported side effects thought to be related to montelukast were:
- Abdominal pain
- Headache

These were usually mild and occurred at a greated frequency in patients treated with montelukast than placebo (a pill containing no medication).

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects at least 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)

Additionally, while the drug has been on the market, the following have been reported:
- upper respiratory infection (*Very common*)
- increased bleeding tendency (*Rare*)
- allergic reactions including rash, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing (*Uncommon*)
- behaviour and mood related changes [dream abnormalities, including nightmares, trouble sleeping, sleep walking, irritability, feeling anxious, restlessness, agitation including aggressive behaviour or hostility, depression (*Uncommon*); tremor (*Rare)*; hallucinations, suicidal thoughts and actions (*Very rare*)]
- dizziness, drowsiness, pins and needles/numbness, seizure (*Uncommon*)
- palpitations (*Rare*)
- nosebleed (*Uncommon*)
- diarrhoea, nausea, vomiting (*Common*); dry mouth, indigestion (*Uncommon*)
- hepatitis (inflammation of the liver) (*Very rare*)
- bruising, itching, hives (*Uncommon*); tender red lumps under the skin most commonly on your shins (erythema nodosum) (*Very rare*)
- joint or muscle pain, muscle cramps (*Uncommon*)
- fever (*Common*); tiredness, feeling unwell, swelling (*Uncommon*).

In asthmatic patients treated with montelukast, very rare cases of a combination of symptoms such as flu-like illness, pins and needles or numbness of arms and legs, worsening of pulmonary symptoms and/or rash (Churg-Strauss syndrome) have been reported. You must tell your doctor right away if you get one or more of these symptoms.

Ask your doctor or pharmacist for more information about side effects.
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 MONTELUKAST 10 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not used after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of the month. Use within 30 days of opening. Once the pack has been opened write the date of opening on the space provided on the package label and also write the date by when the product should be used.

Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions.

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 Montelukast 10 mg Film-coated Tablets contains**

- The active substance is montelukast sodium
- The other ingredients are:

*Core:*

Cellulose microcrystalline
Lactose monohydrate
Croscarmellose sodium
Hydroxypropylcellulose (E463)
Magnesium stearate

*Film-coating:*

Hypromellose (E464)
Hydroxypropylcellulose (E463)
Titanium dioxide (E171)
Iron Oxide yellow (E172)
Carnauba wax (E903)
Iron Oxide red (E172)

**What Montelukast 10 mg Film-coated Tablets looks like and contents of the pack**

10 mg tablets are beige, round, 8 mm biconvex, film-coated tablets, engraved with 'G' on one side and '392'on the other side.

Montelukast 10 mg Film-coated Tablets are available in HDPE containers in cardboard carton with polypropylene child resistant closures also contains a canister of silica gel desiccant.
Pack sizes: 20, 28, 30

Not all pack sizes may be marketed

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
Glenmark Generics (Europe) Limited
Laxmi House, 2-B Draycott Avenue,
Kenton, Harrow, Middlesex, HA3 0BU,
United Kingdom

**Manufacturer**
Glenmark Pharmaceuticals s.r.o.
City Tower, Hvězdova 1716/2b, 140 78 Prague 4,

Czech Republic

Glenmark Generics (Europe) Limited
The Old Sawmill, Hatfield Park,
Hatfield, Hertfordshire, AL9 5PG,
United Kingdom

Accord Healthcare Limited
Sage House, 319 Pinner Road,
Harrow, Middlesex, HA1 4HF,
United Kingdom

This medicinal product is authorised in the member states of the EEA under the following names:

| | |
|---|---|
| Germany | Montelukast Glenmark 10 mg Filmtabletten |
| The Netherlands | Montelukast Glenmark 10 mg Filmomhulde tabletten |

**This leaflet was last approved in** 12/2011.

# Module 4
# Labelling

**The approved labelling text for Montelukast 10 mg Film-coated Tablets is shown below. The Marketing Authorisation Holder is required to submit mock-ups of the labelling to the relevant regulatory authorities for approval before marketing any pack size in a particular member state.**

**PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>**

**HDPE containers with polypropylene child resistant closures with or without a cardboard carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Montelukast 10 mg Film-coated Tablets
montelukast

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains: 10.4 mg montelukast sodium, equivalent to 10 mg montelukast.

**3. LIST OF EXCIPIENTS**

Contains lactose, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

20
28
30

*Not all pack sizes may be marketed*

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP: mm/yyyy

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions. Use within 30 days of opening.

Date opened: dd/mm/yyyy
Do not use after: dd/mm/yyyy

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Glenmark Generics (Europe) Limited
Laxmi House, 2-B Draycott Avenue,
Kenton, Harrow, Middlesex, HA3 0BU,
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 25258/0010

**13. BATCH NUMBER**

Batch: XXXX

**14. GENERAL CLASSIFICATION FOR SUPPLY**

POM

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**Braille Text In Line with Directive 2001/83/EC (amended by Directive 2004/27/EC) Human use, Point 42, article 56a :**

Montelukast 10 mg Film-coated Tablets

# Module 5
# Scientific discussion during initial procedure

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Montelukast 10 mg Film-coated Tablets (PL 25258/0010; UK/H/2273/001/DC) could be approved. This application was submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Germany and the Netherlands as Concerned Member States (CMS).

Montelukast 10 mg Film-coated Tablets is a Prescription-Only Medicine (POM) indicated:

- in the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma.
- in those asthmatic patients in whom montelukast is indicated in asthma, montelukast can also provide symptomatic relief of seasonal allergic rhinitis.
- for the prophylaxis of asthma for patients in which the predominant component is exercise-induced bronchoconstriction.

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Singulair 10 mg film-coated Tablets (Merck Sharp & Dohme B.V, Finland), which has been authorised in the EEA since 25 August 1997. The corresponding reference product in the UK is Singulair 10 mg film-coated tablets (Merck Sharp & Dohme Limited, UK), which was first authorised in January 1998.

Montelukast is an oral cysteinyl leukotriene D4 receptor antagonist indicated as add-on therapy in asthma patients who are inadequately controlled on inhaled corticosteroids and in whom “as needed” short acting β-agonists provided inadequate control of asthma. Montelukast may also be used as an alternative treatment option to low-dose inhaled corticosteroids in patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids. Montelukast is also indicated in prophylaxis of exercise-induced bronchoconstriction.

No new non-clinical studies were conducted, which is acceptable given that the application was for a product that is being considered as a generic medicinal product of an originator product that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support this application, comparing the test product Montelukast 10 mg Film-coated Tablets (Glenmark Generics (Europe) Limited) with the reference product Singulair 10 mg film-coated tablets (Merck Sharp & Dohme Limited, UK)

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was for a product that is being considered as a generic medicinal product of an originator product that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the application could be approved, with the end of procedure (Day 210) on 15 December 2011. After a subsequent national phase, the licence was granted in the UK on 23 February 2012.

# II. ABOUT THE PRODUCT

| | |
|---|---|
| Name of the product in the Reference Member State | Montelukast 10 mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Montelukast sodium |
| Pharmacotherapeutic classification (ATC code) | Other systemic drugs for obstructive airway diseases: Leukotriene receptor antagonist (R03D C03) |
| Pharmaceutical form and strength(s) | 10 mg film-coated tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/2273/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Germany and the Netherlands |
| Marketing Authorisation Number(s) | PL 25258/0010 |
| Name and address of the authorisation holder | Glenmark Generics (Europe) Limited, Laxmi House, 2-B Draycott Avenue, Kenton, Harrow, Middlesex, HA3 0BU, UK. |

# III SCIENTIFIC OVERVIEW AND DISCUSSION

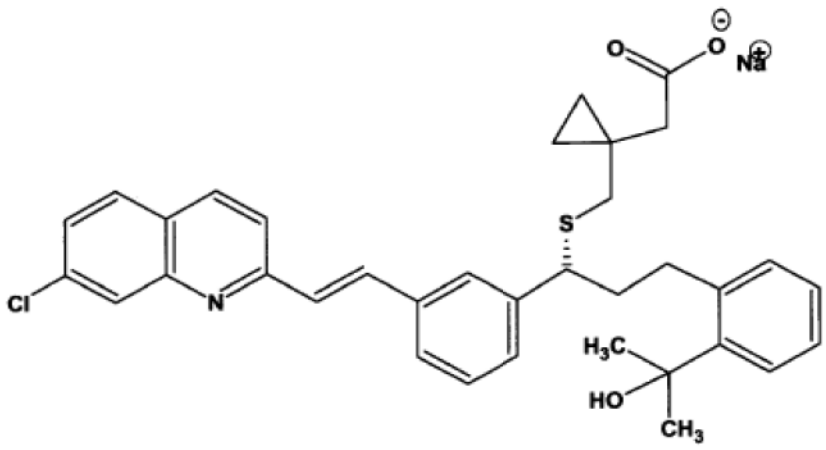
## III.1 QUALITY ASPECTS

### S. Active substance

INN: Montelukast sodium

Chemical name: 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methyl-ethyl)phenyl]propyl]thio]methyl]cyclopropane acetic acid sodium salt.

Structural formula:




**MONTELUKAST SODIUM**

Molecular formula: $C_{35}H_{35}ClNNaO_3S$

Molecular mass: 608.18

Appearance: Off-white to light yellow coloured, hygroscopic powder.

Solubility: Freely soluble in methanol, ethanol and water. Practically insoluble in acetonitrile.

Montelukast sodium is currently not the subject of a European Pharmacopoeia monograph.

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

An appropriate specification is provided for the active 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 active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

## P. Medicinal Product

### Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose (E463), magnesium stearate, hypromellose (E464), hydroxypropylcellulose (E463), titanium dioxide (E171), yellow iron oxide (E172), carnauba wax (E903) and red iron oxide (E172).

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of yellow iron oxide and red iron oxide which are compliant with National Formulary monographs and with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

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

No genetically modified organisms (GMO) have been used in the preparation of this product.

### Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets containing 10 mg montelukast that could be considered as generic medicinal products of Singulair 10 mg film-coated tablets (Merck Sharp & Dohme).

A satisfactory account of the pharmaceutical development has been provided.

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

### Manufacturing Process

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

### Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

### Container-Closure System

All strengths of the finished product are packaged in high density polyethylene (HDPE) containers with a child-resistant closure which also contains a canister of silica gel desiccant with a cardboard outer carton and are available in pack sizes of 20, 28 and 30 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 food.

**Stability of the Product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months for the unopened product which reduces to 30 days after first opening with the storage conditions 'Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions. Use within 30 days of opening.'

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable.

A suitable justification has been provided for not submitting a user test. A bridging report has been provided to justify the absence of a User Testing report. A review of the leaflet shows that the text is consistent with that approved for the reference product. The patients/users are able to act upon the information that the leaflet contains.

**MAA Form**
The MAA form is satisfactory.

**Expert Report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of this application from a pharmaceutical viewpoint.

## III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of montelukast sodium are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical viewpoint.

## III.3 CLINICAL ASPECTS

### Pharmacokinetics

In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

**An open label, balanced, randomised, two-treatment, two-period, two-sequence, two way crossover, single oral dose study to compare the pharmacokinetics of the test product Montelukast 10 mg Film-coated Tablets (Glenmark Generics (Europe) Limited) versus the reference product Singulair 10 mg film-coated tablets (Merck Sharp & Dohme Limited, UK) in healthy adult male volunteers under fasted conditions.**

All volunteers received a single oral dose of either the test or reference product as a 1 x 10 mg tablet administered with 240 ml of water after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The washout period between treatment periods was at least 10 days.

The pharmacokinetic results for montelukast are presented below (log-transformed values; geometric least squares means, ratios and 90% confidence intervals):

| Parameters (Units) | (ln-transformed) Geometric Least Squares Mean | | | 90% Confidence Interval (Parametric) |
|---|---|---|---|---|
| | Test Product-B | Reference Product-A | Ratio (B / A)% | |
| $C_{max}$ (ng / mL) | 547.669 | 499.897 | 109.6 | 100.42– 119.52% |
| $AUC_{0-t}$ (ng.h / mL) | 3138.215 | 2906.088 | 108.0 | 101.22– 115.21% |
| $AUC_{0-\infty}$ (ng.h / mL) | 3220.317 | 2978.780 | 108.1 | 101.50– 115.15% |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration

The 90% confidence intervals for AUC and $C_{max}$ for test versus reference product for montelukast are within predefined acceptance criteria specified in 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

### Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this application.

### Efficacy

No new efficacy data were submitted and none were required for this application.

### Safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

### Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
There are no objections to the approval of this application from a clinical viewpoint.

## IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

**QUALITY**
The quality characteristics of Montelukast 10 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted and none are required for an application of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of montelukast sodium are well-known.

**EFFICACY**
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant's Montelukast 10 mg Film-coated Tablets and its respective reference product (Singulair 10 mg film-coated tablets).

**SAFETY**
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of montelukast sodium is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

**PRODUCT LITERATURE**
The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

**BENEFIT-RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with

montelukast sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |