

Public Assessment Report

Scientific discussion

Montelukast Glenmark 4 mg and 5 mg chewable tablets (montelukast sodium)

NL/H/4810/001-002/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Montelukast Glenmark 4 mg and 5 mg chewable tablets. The procedure was finalised in the United Kingdom (UK/H/2274/001-002/DC). After a transfer in 2019, 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.

Public Assessment Report

Decentralised Procedure

**MONTELUKAST 4 MG CHEWABLE TABLETS
MONTELUKAST 5 MG CHEWABLE TABLETS**

(Montelukast sodium)

Procedure No: UK/H/2274/001-2/DC

UK Licence No: PL 25258/0011 & 0016

GLENMARK GENERICS (EUROPE) LIMITED

LAY SUMMARY

On 15 December 2011, Germany, the Netherlands and the UK agreed to grant Marketing Authorisations to Glenmark Generics (Europe) Limited for the medicinal products Montelukast 4 mg and 5 mg Chewable Tablets (PL 25258/0011 and 16; UK/H/2274/001-2/DC). These licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 22 February 2012.

Montelukast 4 mg Chewable Tablets is a Prescription Only Medicine (POM) for children aged 2 to 5 years old.

Montelukast 5 mg Chewable Tablets is a Prescription Only Medicine (POM) for children and adolescents aged 6 to 14 years old.

Montelukast 4mg and 5mg Chewable Tablets are used for:

- the treatment of asthma in patients who are not adequately controlled on their medication and need additional therapy
- asthma in patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.
- 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 and helps control asthma.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Montelukast 4 mg and 5 mg Chewable Tablets outweigh the risks.

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Module 1

Product Name	Montelukast 4 mg Chewable Tablets Montelukast 5 mg Chewable Tablets
Type of Application	Generic, Article 10(1)
Active Substances	Montelukast sodium
Form	Chewable tablet
Strength	4 mg and 5 mg
MA Holder	Glenmark Generics (Europe) Limited, Laxmi House, 2-B Draycott Avenue, Kenton, Harrow, Middlesex, HA3 0BU, UK.
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Germany and the Netherlands
Procedure Number	UK/H/2274/001-2/DC
Timetable	Day 210 –15 December 2011

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Montelukast 4 mg Chewable Tablets

For children from 2 to 5 years

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One chewable tablet contains 4.2 mg montelukast sodium, which is equivalent to 4 mg montelukast.

Excipient: Aspartame (E951) 1.2 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white, 11 x 7.8 mm oval, biconvex uncoated tablets, with 'G' engraved on one side, and '390' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old 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.

Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old 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 (see section 4.2).

Montelukast is also indicated in the prophylaxis of asthma from 2 years and older in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

This medicinal product is to be given to a child under adult supervision. The dosage for paediatric patients 2-5 years of age is one 4 mg chewable tablet daily to be taken in the evening. If taken in connection with food, montelukast should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary. The montelukast 4 mg chewable tablet formulation is not recommended below 2 years of age.

General recommendations

The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking montelukast even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary 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 as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma

Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients 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 (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Montelukast as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction

In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.

Therapy with montelukast in relation to other treatments for asthma

When treatment with montelukast is used as add-on therapy to inhaled corticosteroids, Montelukast should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

10 mg film-coated tablets are available for adults from the age of 15 years.

5 mg chewable tablets are available for children age 6 to 14 years.

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 doctor's advice as soon as possible if they need more inhalations of short-acting β -agonists than usual.

Montelukast should not be abruptly 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.

Montelukast contains aspartame.

Contains a source of phenylalanine (1.20mg/tablet). May be harmful for children with phenylketonuria.

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 metabolised 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 (eg. paclitaxel, rosiglitazone, and repaglinide).

4.6 Fertility, pregnancy and lactation

Use 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 4,000 adult patients 15 years of age and older
- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age, and
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.

The following drug-related adverse reactions in clinical studies were Common (1/100 to <1/10) in 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)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	headache	headache	
Gastro-intestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

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.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

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	increased bleeding tendency	Rare

system disorders		
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 disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
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
	angioedema	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
<p>*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$).</p> <p>[†]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.</p> <p>[‡]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.</p>		

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 adult 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 overdose 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 antagonists

ATC Code: R03D CO3

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT₁ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD₄ at doses as low as 5 mg. Bronchodilation was observed within two 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 adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV₁ (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 night-time 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 FEV₁: 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 FEV₁: 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 FEV₁ of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulised corticosteroids or inhaled/nebulised sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased 'as needed' beta-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥ 3 consecutive days with daytime symptoms requiring beta-agonist use, or corticosteroids (oral or inhaled), or hospitalisation for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

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 (FEV₁ 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' β -agonist use (-11.7% vs +8.2% change from baseline).

In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:

- FEV₁ increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV₁ was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV₁ was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV₁ was -2.2% with a 95% CI of -3.6, -0.7.
- The percentage of days with β -agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with beta-agonist use was 2.7 with a 95% CI of 0.9, 4.5.
- The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalisation) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
- The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was 7.3% with a 95% CI of 2.9; 11.7.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV₁ 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV₁ 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 6 to 14 years of age (maximal fall in FEV₁ 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV₁ 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 (FEV₁ 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 three 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 two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

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 cytochromes 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), a 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/m² and 30,000 mg/m² 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

Mannitol (E421)
Cellulose microcrystalline
Hydroxypropylcellulose (E463)
Croscarmellose sodium
Cherry flavour
Aspartame (E951)
Magnesium stearate.

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.
- 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 25258/0011
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
22/02/2012
- 10 DATE OF REVISION OF THE TEXT**
22/02/2012

1 NAME OF THE MEDICINAL PRODUCT

Montelukast 5 mg Chewable Tablets

For children from 6 to 14 years

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One chewable tablet contains 5.2 mg montelukast sodium, which is equivalent to 5 mg montelukast.

Excipient: Aspartame (E951) 1.5 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white, 9.5 mm diameter round, biconvex uncoated tablets, with 'G' engraved on one side and '391' on the 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.

Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for 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 (see section 4.2).

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 paediatric patients 6-14 years of age is one 5 mg chewable tablet daily to be taken in the evening. If taken in connection with food, montelukast should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary.

General recommendations:

The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking montelukast even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary 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 as an alternative treatment option to low-dose inhaled corticosteroids for mild persistent asthma:

Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients 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 (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Therapy with montelukast in relation to other treatments for asthma.

When treatment with montelukast is used as add-on therapy to inhaled corticosteroids, montelukast should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

Montelukast 4mg chewable tablets are available for children age 2-5 years.
10 mg tablets are available for adults from the age of 15 years.

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 doctor's advice as soon as possible if they need more inhalations of short-acting β -agonists than usual.

Montelukast should not be abruptly 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.

Montelukast contains aspartame.

Contains a source of phenylalanine (1.50mg/tablet). May be harmful for children with phenylketonuria.

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 oestradiol/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 metabolised 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 (eg., paclitaxel, rosiglitazone, and repaglinide).

4.6 Fertility, pregnancy and lactation

Use 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 4,000 adult patients 15 years of age and older
- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age, and
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.

The following drug-related adverse reactions in clinical studies were Common (1/100 to <1/10) in 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)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	headache	headache	
Gastro-intestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

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.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

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	dizziness, drowsiness	Uncommon

disorder	paraesthesia/hypoesthesia, seizure	
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
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
	angioedema	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
<p>*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$).</p> <p>[†]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.</p> <p>[‡]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.</p>		

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 adult 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 overdose 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 antagonists

ATC Code: R03D CO3

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT₁ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD₄ at doses as low as 5 mg. Bronchodilation was observed within two 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 adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV₁ (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 night-time 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 FEV₁: 5.43% vs 1.04%; β-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 FEV₁: 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 FEV₁ of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulised corticosteroids or inhaled/nebulised sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased 'as needed' beta-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥ 3 consecutive days with daytime symptoms requiring beta-agonist use, or corticosteroids (oral or inhaled), or hospitalisation for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

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 (FEV₁ 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).

In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both

montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:

- FEV₁ increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV₁ was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV₁ was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV₁ was -2.2% with a 95% CI of -3.6, -0.7.
- The percentage of days with β -agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β -agonist use was 2.7 with a 95% CI of 0.9, 4.5.
- The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalisation) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
- The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was 7.3% with a 95% CI of 2.9; 11.7.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV₁ 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV₁ 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 6 to 14 years of age (maximal fall in FEV₁ 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV₁ 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 (FEV₁ 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 three 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 two hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

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 cytochromes 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), a 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/m² and 30,000 mg/m² 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

Mannitol (E421)
Cellulose microcrystalline
Hydroxypropylcellulose (E463)
Croscarmellose sodium
Cherry flavour
Aspartame (E951)
Magnesium stearate

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 25258/0016
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
22/02/2012
- 10 DATE OF REVISION OF THE TEXT**
22/02/2012

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 4mg Chewable Tablets
montelukast
For children from 2 to 5 years

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 4 mg Chewable Tablets is and what it is used for
2. Before you take Montelukast 4 mg Chewable Tablets
3. How to take Montelukast 4 mg Chewable Tablets
4. Possible side effects
5. How to store Montelukast 4 mg Chewable Tablets
6. Further information

1. WHAT MONTELUKAST 4 MG CHEWABLE TABLETS IS AND WHAT IT IS USED FOR

Montelukast 4 mg Chewable Tablets is a Leukotriene receptor antagonist that blocks the substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs. By blocking leukotrienes, Montelukast 4 mg Chewable Tablets improves and controls the symptoms of asthma.

Your doctor has prescribed Montelukast 4 mg Chewable Tablets to treat asthma, preventing your asthma symptoms during the day and night.

- Montelukast 4 mg Chewable Tablets is used for the treatment of 2 to 5 year old patients who are not adequately controlled on their medication and need additional therapy.
- Montelukast 4 mg Chewable Tablets also helps prevent the narrowing of airways triggered by exercise for patients 2 years of age and older.
- Montelukast 4 mg Chewable Tablets may also be used as an alternative treatment to inhaled corticosteroids for 2 to 5 year old patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.

Your doctor will determine how Montelukast 4 mg Chewable Tablets should be used depending on the symptoms and severity of you or your child's asthma.

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.

2. BEFORE YOU TAKE MONTELUKAST 4 MG CHEWABLE TABLETS

Tell your doctor about any medical problems or allergies your child has now or has had.

Do not take Montelukast 4 mg Chewable Tablets

- If your child is allergic (hypersensitive) to montelukast or any of the other ingredients of Montelukast 4 mg Chewable Tablets (see Section 6, “further information”)

Take special care with Montelukast 4 mg Chewable Tablets

- If your child’s asthma or breathing gets worse, tell your doctor immediately.
- Oral Montelukast 4 mg Chewable Tablets is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you for your child. Always have your inhaled rescue medicine for asthma attacks with you.
- It is important that your child take all asthma medications prescribed by your doctor, Montelukast 4 mg Chewable Tablets should not be used instead of other asthma medications your doctor has prescribed for your child.
- If your child is on anti-asthma medicines be aware that if he/she develops 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.
- Your child should not take aspirin or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make her/his asthma worse.

Taking other medicines

Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. Some medicines may affect how montelukast works, or montelukast may affect how other medicines work.

Treatment with Montelukast 4 mg Chewable Tablets can be affected by other medicines. Tell your doctor if your child is 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 4 mg Chewable Tablets with food and drink

Montelukast 4 mg Chewable Tablets should not be taken immediately with food; it should be taken at least 1 hour before or two hours after food.

Pregnancy and breast-feeding

This subsection is not applicable for Montelukast 4 mg Chewable Tablets since they are intended for use in children 2 to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

Use in Pregnancy

Women who are pregnant or intend to become pregnant should consult their doctor before taking Montelukast 4 mg Chewable Tablets. Your doctor will assess whether you can take Montelukast 4 mg Chewable Tablets during this time.

Use in breast-feeding

It is not known if Montelukast 4 mg Chewable Tablets appears in breast milk. You should consult your doctor before taking Montelukast 4 mg Chewable Tablets if you are breast feeding or if you are planning to breast feed.

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

Driving and using machines

This subsection is not applicable for Montelukast 4 mg Chewable Tablets since they are intended for use in children 2 to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

Montelukast is not expected to affect your ability to drive a car or operate machinery. However, individual responses in medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with montelukast may affect some patients' ability to drive or operate machinery.

Important information about some of the ingredients of Montelukast 4 mg Chewable Tablets

Montelukast 4mg Chewable Tablets contain aspartame, a source of phenylalanine. If your child has phenylketonuria (a rare, hereditary disorder of the metabolism) you should take into account that each tablet contains phenylalanine (equivalent to 1.20 mg/tablet).

3. HOW TO TAKE MONTELUKAST 4 MG CHEWABLE TABLETS

This medicine is to be given to a child under adult supervision.

- Your child should take only one tablet of Montelukast 4 mg Chewable Tablets once a day as prescribed by your doctor.
- It should be taken even when your child has no symptoms or has an acute asthma attack.
- Always have your child take Montelukast 4 mg Chewable Tablets as your doctor has told you. You should check with your child's doctor or pharmacist if you are not sure.
- To be taken by mouth

For Children aged 2 to 5 years of age:

One Montelukast 4 mg Chewable Tablets to be taken daily in the evening. Montelukast 4 mg Chewable Tablets should not be taken immediately with food; it should be taken at least 1 hour before or two hours after food.

If your child is taking Montelukast 4 mg Chewable Tablets, make sure that he/she does not take any other medicines that contain the same active ingredient montelukast.

Other available strength/pharmaceutical form:

Montelukast 5 mg Chewable Tablets are available for children age 6 to 14 years.

If your child takes more Montelukast 4 mg Chewable Tablets than you should

If you or your child takes more Montelukast 4 mg Chewable Tablets than you should contact your doctor or pharmacist immediately.

There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity (unusually active).

If you forget to give Montelukast 4 mg Chewable Tablets to your child

Try to give Montelukast 4 mg Chewable Tablets as prescribed. However, if your child misses a dose, just resume the usual schedule of one tablet once daily. Do not give a double dose to make up for a forgotten dose.

If your child stops taking Montelukast 4 mg Chewable Tablets

Montelukast 4 mg Chewable Tablets can treat your child's asthma only if you or your child continues to take it. It is important for your child to continue taking Montelukast 4 mg Chewable Tablets for as long as your doctor prescribes. It will help control your child's 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 4 mg Chewable Tablets can cause side effects, although not everybody gets them.

In clinical studies with montelukast 4 mg chewable tablets, 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 4 mg chewable tablets were:

- abdominal pain
- thirst

Additionally, the following side effect was reported in clinical studies with montelukast 10 mg film-coated tablets and 5 mg chewable tablets:

- headache

These were usually mild and occurred at a greater 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 more than 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 your child gets 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 4 MG CHEWABLE TABLETS

Keep out of the reach and sight of children.

Do not use 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 4 mg Chewable Tablets contains

- The active substance is montelukast sodium
- The other ingredients are:
 - Mannitol [E421]
 - Cellulose microcrystalline
 - Hydroxypropylcellulose [E463]
 - Croscarmellose sodium
 - Cherry flavour
 - Aspartame [E951]
 - Magnesium stearate.

What Montelukast 4 mg Chewable Tablets looks like and contents of the pack

4 mg chewable tablets are white to off-white, 11 x 7.8mm oval, biconvex uncoated tablets, with 'G' engraved on one side, and '390' on the other side.

The tablets are packed in HDPE containers which includes a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

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 Generics 4mg Kautabletten
The Netherlands	Montelukast Glenmark 4mg Kauwtabletten

This leaflet was last approved in 12/2011.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Montelukast 5mg Chewable Tablets
montelukast
For children from 6 to 14 years

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 5 mg Chewable Tablets is and what it is used for
2. Before you take Montelukast 5 mg Chewable Tablets
3. How to take Montelukast 5 mg Chewable Tablets
4. Possible side effects
5. How to store Montelukast 5 mg Chewable Tablets
6. Further information

1. WHAT MONTELUKAST 5 MG CHEWABLE TABLETS IS AND WHAT IT IS USED FOR

Montelukast 5 mg Chewable Tablets is a Leukotriene receptor antagonist that blocks the substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs. By blocking leukotrienes, Montelukast 5 mg Chewable Tablets improves and controls the symptoms of asthma.

Your doctor has prescribed Montelukast 5 mg Chewable Tablets to treat asthma, preventing your asthma symptoms during the day and night.

- Montelukast 5 mg Chewable Tablets is used for the treatment of patients who are not adequately controlled on their medication and need additional therapy.
- Montelukast 5 mg Chewable Tablets also helps prevent the narrowing of airways triggered by exercise.
- Montelukast 5 mg Chewable Tablets may also be used as an alternative treatment to inhaled corticosteroids for 6 to 14 year old patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.

Your doctor will determine how Montelukast 5 mg Chewable Tablets should be used depending on the symptoms and severity of you or your child's asthma.

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.

2. BEFORE YOU TAKE MONTELUKAST 5 MG CHEWABLE TABLETS

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

Do not take Montelukast 5 mg Chewable Tablets

- If your child is allergic (hypersensitive) to montelukast or any of the other ingredients of Montelukast 5 mg Chewable Tablets (see Section 6, "further information")

Take special care with Montelukast 5 mg Chewable Tablets

- If your child's asthma or breathing gets worse, tell your doctor immediately.
- Oral Montelukast 5 mg Chewable Tablets is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you for your child. Always have your inhaled rescue medicine for asthma attacks with you.
- It is important that your child takes all asthma medications prescribed by your doctor. Montelukast 5 mg Chewable Tablets should not be used instead of other asthma medications your doctor has prescribed for your child.
- 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.
- Your child should not take aspirin or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make her/his asthma worse.

Taking other medicines

Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. Some medicines may affect how montelukast works, or montelukast may affect how other medicines work.

Treatment with Montelukast 5 mg Chewable Tablets can be affected by other medicines. Tell your doctor if your child is 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 5 mg Chewable Tablets with food and drink

Montelukast 5 mg Chewable Tablets should not be taken immediately with food; it should be taken at least 1 hour before or two hours after food.

Pregnancy and breast-feeding*Use in Pregnancy*

Women who are pregnant or intend to become pregnant should consult their doctor before taking Montelukast 5 mg Chewable Tablets. Your doctor will assess whether you can take Montelukast 5 mg Chewable Tablets during this time.

Use in breast-feeding

It is not known if Montelukast 5 mg Chewable Tablets appears in breast milk. You should consult your doctor before taking Montelukast 5 mg Chewable Tablets if you are breast feeding or if you are planning to breast feed.

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

Driving and using machines

Montelukast is not expected to affect your ability to drive a car or operate machinery. However, individual responses in medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with montelukast may affect some patients' ability to drive or operate machinery.

Important information about some of the ingredients of Montelukast 5 mg Chewable Tablets

Montelukast 5mg Chewable Tablets contain aspartame, a source of phenylalanine. If your child has phenylketonuria (a rare, hereditary disorder of the metabolism) you should take into account that each tablet contains phenylalanine (equivalent to 1.50 mg/tablet).

3. HOW TO TAKE MONTELUKAST 5 MG CHEWABLE TABLETS

- You or your child should take only one tablet of Montelukast 5 mg Chewable Tablets once a day as prescribed by your doctor.
- It should be taken even when you or your child has no symptoms or has an acute asthma attack.
- Always take Montelukast 5 mg Chewable Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- To be taken by mouth

For Children aged 6 to 14 years of age:

One Montelukast 5 mg Chewable Tablets to be taken daily in the evening. Montelukast 5 mg Chewable Tablets should not be taken immediately with food; it should be taken at least 1 hour before or two hours after food.

If your child is taking Montelukast 5 mg Chewable Tablets make sure that he/she does not take any other medicines that contain the same active ingredient montelukast.

Other available strength/pharmaceutical form:

Montelukast 4 mg Chewable Tablets are available for children for children age 2-5 years.

If you or your child take more Montelukast 5 mg Chewable Tablets than you should

If you or your child takes more Montelukast 5 mg Chewable Tablets than you should contact your doctor or pharmacist immediately.

There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity (unusually active).

If you forget to take Montelukast 5 mg Chewable Tablets or give Montelukast 5 mg Chewable Tablets to your child

Try to take Montelukast 5 mg Chewable Tablets as prescribed. However, if your child misses a dose, just resume the usual schedule of one tablet once daily. Do not take a double dose to make up for a forgotten dose.

If your child stops taking Montelukast 5 mg Chewable Tablets

Montelukast 5 mg Chewable Tablets can treat your child's asthma only if you or your child continues to take it. It is important to continue taking Montelukast 5 mg Chewable Tablets for as long as your doctor prescribes. It will help control your child's 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 5 mg Chewable Tablets can cause side effects, although not everybody gets them.

In clinical studies with montelukast 5 mg chewable tablets, 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:

- headache

Additionally, the following side effect was reported in clinical studies with montelukast 10 mg film-coated tablets:

- abdominal pain

These were usually mild and occurred at a greater 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 your child gets 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 5 MG CHEWABLE TABLETS

Keep out of the reach and sight of children.

Do not use 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 5 mg Chewable Tablets contains

- The active substance is montelukast sodium
- The other ingredients are:
 - Mannitol [E421]
 - Cellulose microcrystalline
 - Hydroxypropylcellulose [E463]
 - Croscarmellose sodium
 - Cherry flavour
 - Aspartame [E951]
 - Magnesium stearate.

What Montelukast 5 mg Chewable Tablets looks like and contents of the pack

5mg chewable tablets are white to off white, 9.5 mm diameter round, biconvex uncoated tablets, engraved with 'G' on one side and '391' on the other side.

The tablets are packed in HDPE containers which includes a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

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 Generics 5mg Kautabletten
The Netherlands	Montelukast Glenmark 5mg Kauwtabletten

This leaflet was last approved in 12/2011.

Module 4

Labelling

The approved labelling text for Montelukast 4 mg and 5 mg Chewable 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 a cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

Montelukast 4 mg Chewable Tablets
montelukast
For children from 2 to 5 years

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 4 mg chewable tablet contains: 4.2 mg montelukast sodium, equivalent to 4 mg montelukast

3. LIST OF EXCIPIENTS

Contains Aspartame, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Chewable 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 25258/0011

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 4 mg Chewable Tablets

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

HDPE containers with polypropylene child resistant closures with a cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

Montelukast 5 mg Chewable Tablets
 Montelukast
 For children from 6 to 14 years

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5mg chewable tablet contains: 5.2 mg montelukast sodium, equivalent to 5 mg montelukast

3. LIST OF EXCIPIENTS

Contains Aspartame, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Chewable 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 25258/0016

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 5mg Chewable 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 applications for Montelukast 4 mg and 5 mg Chewable Tablets (PL 25258/0011 and 16; UK/H/2274/001-2/DC) could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Germany and the Netherlands as Concerned Member States (CMS).

Montelukast 4 mg chewable tablets is a Prescription-Only Medicine (POM) for children aged 2 to 5 years old, whereas Montelukast 5 mg chewable tablets is a POM for children and adolescents aged 6 to 14 years old.

Montelukast 4 mg and 5 mg Chewable Tablets are 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.
- 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 (see section 4.2 of SmPC).
- for the prophylaxis of asthma for patients in which the predominant component is exercise-induced bronchoconstriction.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Singulair 5 mg chewable tablets (Merck Sharp & Dohme, Finland), which has been authorised in the EEA since 25 August 1997. The corresponding reference products in the UK are Singulair Paediatric 4 mg and 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK), which were first authorised in January 2001 and January 1998 respectively.

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 applications were for products that are being considered as generic medicinal products 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 5 mg chewable tablets (Glenmark Generics (Europe) Limited)

with the reference product Singulair Paediatric 5 mg Chewable 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 applications were for products that are being considered as generic medicinal products 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 applications could be approved, with the end of procedure (Day 210) on 15 December 2011. After a subsequent national phase, the licences were granted in the UK on 22 February 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Montelukast 4 mg Chewable Tablets Montelukast 5 mg Chewable 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)	4mg and 5mg chewable tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2274/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Germany and the Netherlands
Marketing Authorisation Number(s)	PL 25258/0011 and 0016
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

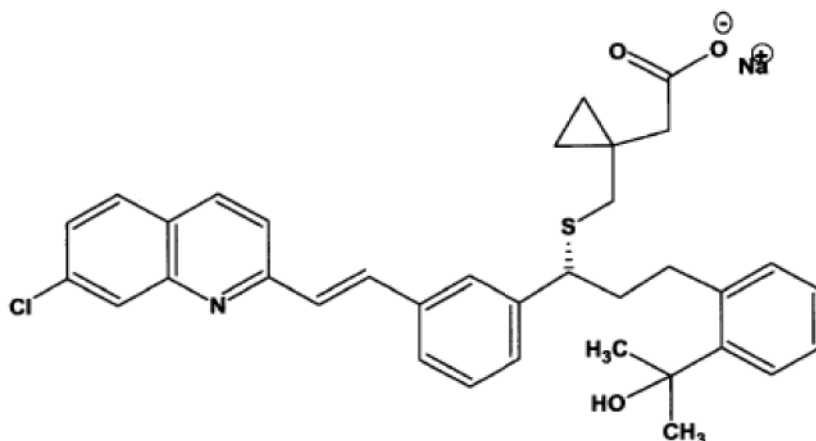
III.1 QUALITY ASPECTS

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 mannitol (E421), microcrystalline cellulose, hydroxypropyl cellulose (E463), croscarmellose sodium, cherry flavour, aspartame (E951) and magnesium stearate

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of cherry flavour, which is compliant with a suitable in-house specification. In addition, the cherry flavour is in compliance with current EEC directives concerning the use of flavouring in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets containing 4 mg and 5 mg montelukast that could be considered as generic medicinal products of Singulair Paediatric 4mg and 5mg Chewable 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 Forms

The MAA forms are 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 these applications 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 these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, balanced, randomised, single-dose, two-treatment, two-period, two-sequence, two way, crossover study to compare the pharmacokinetics of the test product Montelukast 5 mg chewable tablets (Glenmark Generics (Europe) Limited) versus the reference product Singulair Paediatric 5 mg Chewable 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 5 mg tablet administered with 240 ml of water under fasting conditions. Each of the subjects was instructed to chew the tablet completely and then swallow it with 240 ml of water after proper gargling. 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 7 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)	312.559	310.295	100.7	94.05– 107.88%
AUC_{0-t} (ng.h / mL)	1639.502	1631.568	100.5	97.35– 103.72%
$AUC_{0-\infty}$ (ng.h / mL)	1691.609	1683.974	100.5	97.35– 103.66%

$AUC_{0-\infty}$ 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.

As the 4 mg and 5 mg strength of the product meet the criteria specified in Guideline on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 4 mg strength.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy

No new efficacy data were submitted and none were required for these applications.

Safety

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

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

Labels

The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. 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 these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The quality characteristics of Montelukast 4 mg and 5 mg Chewable 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 applications 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 applications of this type.

Bioequivalence has been demonstrated between the applicant's Montelukast 5 mg Chewable Tablets and its respective reference product (Singulair Paediatric 5 mg Chewable tablets). As the 4 mg and 5 mg strength of the product meets the biowaiver criteria specified in the 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 4 mg strength.

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 SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products 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