Public Assessment Report

Decentralised Procedure

MONTELUKAST 4 MG GRANULES

(Montelukast sodium)

Procedure No: UK/H/2593/001/DC

UK Licence No: PL 13931/0052

CHANELLE MEDICAL
LAY SUMMARY

On 20 July 2011, Bulgaria, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Poland, Sweden, Slovakia and the UK agreed to grant a Marketing Authorisation to Chanelle Medical for the medicinal product Montelukast 4 mg granules (PL 13931/0052; UK/H/2593/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 18 August 2011.

Montelukast 4 mg granules is a Prescription Only Medicine (POM) used to treat asthma in children, preventing asthma symptoms during the day and night.

This medicine is used:

- for the treatment of 6 months to 5 year old patients who are not adequately controlled on their medication and need additional therapy
- as an alternative 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.
- to help prevent the narrowing of airways triggered by exercise for patients 2 years of age and older.

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 help control asthma.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Montelukast 4 mg granules outweigh the risks.
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Module 5: Scientific Discussion

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## Module 1

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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<td><strong>MA Holder</strong></td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Montelukast 4 mg granules
For children from 6 months to 5 years of age

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One sachet of granules contains montelukast sodium, which is equivalent to 4 mg montelukast. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Granules
White to off-white granules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Montelukast granules are indicated in the treatment of asthma as add-on therapy in those 6 months 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 granules 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 granules are also indicated in the prophylaxis of asthma from 2 years of age 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 6 months to 5 years of age is one sachet of 4-mg granules daily to be taken in the evening. No dosage adjustment within this age group is necessary. Efficacy data from clinical trials in paediatric patients 6 months to 2 years of age with persistent asthma are limited. Patients should be evaluated after 2 to 4 weeks for response to montelukast treatment. Treatment should be discontinued if a lack of response is observed. The Montelukast 4 mg Granules formulation is not recommended below 6 months of age.

Administration of Montelukast granules:
Montelukast granules can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce, ice cream, carrots and rice). The sachet should not be opened until ready to use. After opening the sachet, the full dose of Montelukast granules must be administered immediately (within 15 minutes). If mixed with food, Montelukast granules must not be stored for future use. Montelukast granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. Montelukast granules can be administered without regard to the timing of food ingestion.

General recommendations. The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking Montelukast granules 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 granules 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 2 to 5 years old 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 that 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 granules 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 granules in relation to other treatments for asthma.

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

Other available strength/pharmaceutical forms:

10-mg film-coated tablets are available for adults 15 years of age and older.
5-mg chewable tablets are available for paediatric patients 6 to 14 years of age.
4-mg chewable tablets are available as an alternative formulation for paediatric patients 2 to 5 years of age.

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

4.4 Special warnings and precautions for use
The diagnosis of persistent asthma in very young children (6 months – 2 years) should be established by a paediatrician or pulmonologist.

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 beta agonist should be used. Patients should seek their doctors’ advice as soon as possible if they need more inhalations of short-acting beta-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. 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.

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 medicinal products: 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 medicinal products 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 medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

4.6 Pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/fetal 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 may be used during pregnancy only if it is considered to be clearly essential.

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 granules may be used in breast-feeding mothers only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

Montelukast is not expected to affect a patient’s ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10-mg film-coated tablets in approximately 4000 adult patients 15 years of age and older
- 5-mg chewable tablets in approximately 1750 paediatric patients 6 to 14 years of age
- 4-mg chewable tablets in 851 paediatric patients 2 to 5 years of age, and
- 4-mg granules in 175 paediatric patients 6 months to 2 years of age.

Montelukast has been evaluated in a clinical study in patients with intermittent asthma as follows: 4 mg granules and chewable tablets in 1038 paediatric patients 6 months to 5 years of age

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

<table>
<thead>
<tr>
<th>Body System Class</th>
<th>Adult Patients</th>
<th>Paediatric Patients</th>
<th>Paediatric Patients</th>
<th>Paediatric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 years and older</td>
<td>6 to 14 years old</td>
<td>2 to 5 years old</td>
<td>6 months up to 2 years old</td>
</tr>
<tr>
<td></td>
<td>(two 12-week studies; n=795)</td>
<td>(one 8-week study; n=201)</td>
<td>(one 12-week study; n=461)</td>
<td>(one 6-week study; n=175)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache studies; n=615)</td>
<td>study; n=278)</td>
<td>hyperkinesia</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>headache</td>
<td></td>
<td>asthma</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>abdominal pain</td>
<td>abdominal pain</td>
<td>diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Eczematous dermatitis, rash</td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td>thirst</td>
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</tr>
</tbody>
</table>

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.

The safety profile in paediatric patients 6 months to 2 years of age did not change with treatment up to 3 months.

The following adverse reactions have been reported in post-marketing use:

**Infections and infestations:** upper respiratory infection.

**Blood and lymphatic system disorders:** increased bleeding tendency.

**Immune system disorders:** hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

**Psychiatric disorders:** dream abnormalities including nightmares, hallucinations, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, tremor, depression, suicidal thinking and behaviour (suicidality) in very rare cases.

**Nervous system disorders:** dizziness drowsiness, paraesthesia/hypoesthesia, seizure.

**Cardiac disorders:** palpitations.

**Respiratory, thoracic and mediastinal disorders:** epistaxis.

**Gastro-intestinal disorders:** diarrhoea, dry mouth, dyspepsia, nausea, vomiting.

**Hepatobiliary disorders:** elevated levels of serum transaminases (ALT, AST), hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).

**Skin and subcutaneous tissue disorders:** angioedema, bruising, urticaria, pruritus, rash, erythema nodosum.

**Musculoskeletal and connective tissue disorders:** arthralgia, myalgia including muscle cramps.

**General disorders and administration site conditions:** asthenia/fatigue, malaise, oedema, pyrexia.

Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients (see section 4.4).

### 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. 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonist, ATC code: R03D C03

The cysteinyl leukotrienes (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, mucus 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 2 hours of oral administration. The bronchodilation effect caused by a beta agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). 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 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 noninferior 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 change 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 significant: - 2.2% with a 95% CI of - 3.6, - 0.7.

The percentage of days with beta-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 significant: 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 significant: 7.3% with a 95% CI of 2.9; 11.7.

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 ≤ 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 a placebo-controlled study in paediatric patients 6 months to 5 years of age who had intermittent asthma but did not have persistent asthma, treatment with montelukast was administered over a 12-month period, either as a once-daily 4 mg regimen or as a series of 12-day courses that each were started when an episode of intermittent symptoms began. No significant difference was observed between patients treated with montelukast 4 mg or placebo in the number of asthma episodes culminating in an asthma attack, defined as an asthma episode requiring utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid.

Efficacy of montelukast is supported in paediatric patients 6 months to 2 years of age by extrapolation from the demonstrated efficacy in patients 2 years of age and older with asthma, and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the medicinal product's effect are substantially similar among these populations.

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 ($C_{\text{max}}$) is achieved 3 hours ($T_{\text{max}}$) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and $C_{\text{max}}$ 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 $C_{\text{max}}$ is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

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

The 4-mg granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. In paediatric patients 6 months to 2 years of age, $C_{\text{max}}$ is achieved 2 hours after administration of the 4-mg granules formulation. $C_{\text{max}}$ is nearly 2-fold greater than in adults receiving a 10-mg tablet. The co-administration of applesauce or a high-fat standard meal with the granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC (1225.7 vs 1223.1 ng.hr/mL with and without applesauce, respectively, and 1191.8 vs 1148.5 ng.hr/mL with and without a high-fat standard meal, respectively).

**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 postdose were minimal in all other tissues.

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

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

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

**Characteristics in patients.** No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), 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 (Pearlitol 50C)
Hydroxypropyl cellulose (Klucel LF)
Sodium laurilsulfate
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container
Packaged in Claycoated kraft / LDPE / Al / Surlyn sachet in:
Cartons of 7, 20, 28 and 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Chanelle Medical, Loughrea, Co. Galway, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2011

10 DATE OF REVISION OF THE TEXT
18/08/2011
Module 3

The following text is the approved Patient Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Montelukast 4 mg granules
For children from 6 months to 5 years of age

Read all of this leaflet carefully before your child starts 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 your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child’s.
- 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 granules are and what they are used for
2. Before Montelukast granules are taken
3. How to take Montelukast granules
4. Possible side effects
5. How to store Montelukast granules
6. Further information

1. WHAT MONTELUKAST GRANULES ARE AND WHAT THEY ARE USED FOR

Montelukast granules are a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs. By blocking leukotrienes, Montelukast granules improve asthma symptoms and help control asthma.

Your doctor has prescribed Montelukast granules to treat your child’s asthma, preventing asthma symptoms during the day and night.

- Montelukast granules are used for the treatment of 6 months to 5 year old patients who are not adequately controlled on their medication and need additional therapy.
- Montelukast granules 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.
- Montelukast granules also help prevent the narrowing of airways triggered by exercise for patients 2 years of age and older.

Your doctor will determine how Montelukast granules should be used depending on the symptoms and severity of 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 MONTELUKAST GRANULES ARE TAKEN

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

Do NOT give Montelukast granules to your child if he/she
- is allergic (hypersensitive) to montelukast sodium or any of the other ingredients of Montelukast granules (see 6. Further information)

Take special care with Montelukast granules
- If your child’s asthma or breathing gets worse, tell your doctor immediately.
- Oral Montelukast granules are 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 child’s inhaled rescue medicine for asthma attacks with you.
- It is important that your child take all asthma medications prescribed by your doctor. Montelukast granules 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 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 acetylsalicylic acid (aspirin) or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make his/her asthma worse.

Taking other medicines
Some medicines may affect how Montelukast granules work. or Montelukast granules may affect how your child’s other medicines work.

Please tell your doctor or pharmacist if your child is taking or has recently taken other medicines, including those obtained without a prescription.

Tell your doctor if your child is taking the following medicines before starting Montelukast granules:
- phenobarbital (used for treatment of epilepsy)
- phenytoin (used for treatment of epilepsy)
- rifampicin (used to treat tuberculosis and some other infections)

Taking Montelukast granules with food and drink
Montelukast granules can be taken without regard to the timing of food intake.

Pregnancy and breast-feeding
This subsection is not applicable for Montelukast 4 mg granules since they are intended for use in children 6 months 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. Your doctor will assess whether you can take montelukast during this time.

Use in breast-feeding

It is not known if montelukast appears in breast milk. You should consult your doctor before taking montelukast if you are breast-feeding or intend to breast-feed.
Driving and using machines
This subsection is not applicable for Montelukast 4 mg granules since they are intended for use in children 6 months to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

Montelukast has minor influence on the ability to drive and use machines. However, individual responses to 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.

3. HOW TO TAKE MONTELUKAST GRANULES

- This medicine is to be given to a child under adult supervision. Your child should take Montelukast granules every evening.
- It should be taken even when your child has no symptoms or if he/she has an acute asthma attack.
- Always have your child take Montelukast granules 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 6 months to 5 years of age:
One sachet of Montelukast 4 mg granules to be taken by mouth each evening.

If your child is taking Montelukast granules, be sure that your child does not take any other products that contain the same active ingredient, montelukast.

For children 6 months to 2 years old, Montelukast 4 mg granules are available.
For children 2 to 5 years old, Montelukast 4 mg chewable tablets and Montelukast 4 mg granules are available. The Montelukast 4 mg granules formulation is not recommended below 6 months of age.

How should I give Montelukast 4 mg granules to my child?

- Do not open the sachet until ready to use.

- Montelukast granules can be given either:
  - directly in the mouth;
  - OR mixed with a spoonful of cold or room temperature soft food (for example, applesauce, ice cream, carrots and rice).

- Mix all of the contents of the Montelukast granules into a spoonful of cold or room temperature soft food. taking care to see that the entire dose is mixed with the food.

- Be sure the child is given the entire spoonful of the granule/food mixture immediately (within 15 minutes). IMPORTANT: Never store any granule/food mixture for use at a later time.

- Montelukast granules are not intended to be dissolved in liquid. However, your child may take liquids after swallowing the Montelukast granules.

- Montelukast granules can be taken without regard to the timing of food intake.

If your child takes more Montelukast granules than he/she should
Contact your child’s doctor immediately for advice.

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.

If you forget to give Montelukast granules to your child
Try to give Montelukast granules as prescribed. However, if your child misses a dose, just resume the usual schedule of one sachet once daily.

Do not give a double dose to make up for a forgotten dose.

If your child stops taking Montelukast granules
Montelukast granules can treat your child’s asthma only if he/she continues taking it. It is important for your child to continue taking Montelukast granules 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 child’s doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Montelukast granules can cause side effects, although not everybody gets them.

The following terms are used to describe how often side effects have been reported:

<table>
<thead>
<tr>
<th>Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>common</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>uncommon</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>rare</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>very rare</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>not known</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

In clinical studies with montelukast 4 mg granules, the most commonly reported side effects (occurring in at least 1 of 100 patients and less than 1 of 10 paediatric patients treated) thought to be related to montelukast were:

- diarrhoea
- hyperactivity
- asthma
- scaly and itchy skin
- rash

Additionally, the following side effects were reported in clinical studies with either montelukast 10 mg film-coated tablets or montelukast 5 mg or 4 mg chewable tablets:

- abdominal pain
- headache
- thirst

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

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

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 child’s doctor or pharmacist.**

5. **HOW TO STORE MONTELUKAST GRANULES**

Keep out of the reach and sight of children.

Do not use this medicine after the date shown on the sachet after EXP. The first two numbers indicate the month; the last four numbers indicate the year. This medicine expires at the end of the month shown.

Store in the original package in order to protect from light and moisture.

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 granules contain**
- The active substance is montelukast. Each sachet of granules contains montelukast sodium which corresponds to 4 mg montelukast.
- The other ingredients are mannitol, hydroxypropyl cellulose, sodium laurylsulfate and magnesium stearate

**What Montelukast granules look like and contents of the pack**
Montelukast 4 mg granules are white to off-white granules.
Cartons of 7, 20, 28 and 30 sachets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Chanelle Medical, Loughrea, Co. Galway, Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

BG: Ephyra 4 mg granules
DE: Montelukast-CT 4 mg Granulat
EL: Montelukast Teva 4 mg Kökxiá
ES: Montelukast Teva 4 mg granulado EFG
FI: Montelukast Teva
FR: Montelukast Teva
HU: Montelukast-Teva
IE: Montelukast Teva
IT: Montelukast Dorom
NO: Montelukast Teva
PL: Drimon
SE: Motelukast Teva
SK: Montelukast Teva 4 mg granulát
UK: Montelukast

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]
Module 4
Labelling

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Montelukast 4 mg granules
For children 6 months to 5 years of age

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One sachet of granules contains montelukast sodium, which is equivalent to 4 mg montelukast

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules
7 sachets
20 sachets
28 sachets
30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Please read the enclosed 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
9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

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

Chanelle Medical, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 13931/0052

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Montelukast 4 mg granules
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Montelukast 4 mg granules
For children 6 months to 5 years of age
Oral use

2. METHOD OF ADMINISTRATION

Please read the enclosed package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Chanelle Medical

Store in the original package in order to protect from light and moisture.
Keep out of the reach and sight of children.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Montelukast 4 mg granules (PL 13931/0052; UK/H/2593/001/DC) could be approved. This application was submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Bulgaria, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Poland, Sweden and Slovakia as Concerned Member States (CMS).

Montelukast 4 mg granules is a Prescription-Only Medicine (POM) indicated:

- in the treatment of asthma as add-on therapy in those 6 months 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.
- as 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 of SmPC).
- for the prophylaxis of asthma from 2 years of age and older for in which the predominant component is exercise-induced bronchoconstriction.

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Singulair Paediatric 4mg Granules (PL 00025/0440) which was first licensed in the UK to Merck Sharp & Dohme Limited, on 14 February 2003. The originator product is Singulair 5 mg Chewable Tablets, authorised to Merck Sharp & Dohme Limited in Finland on 25 August 1997. The originator product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

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 beta agonists provided inadequate control of asthma.

Montelukast may also be used as an alternative treatment option to low-dose inhaled corticosteroids in patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids. Montelukast is also indicated in prophylaxis of exercise-induced bronchoconstriction.

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

One bioequivalence study (single dose) was submitted to support this application, comparing the test product Montelukast 4 mg granules with the reference product Singulair 4 mg Granules (Merck Sharp & Dohme BV, Netherlands)

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

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

The RMS and CMS considered that the application could be approved, with the end of procedure (Day 210) on 20 July 2011. After a subsequent national phase, the licence was granted in the UK on 18 August 2011.
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Montelukast 4 mg granules |
| 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) | 4 mg granules |
| Reference numbers for the Mutual Recognition Procedure | UK/H/2593/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Bulgaria, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Poland, Sweden and Slovakia |
| Marketing Authorisation Number(s) | PL 13931/00052 |
| Name and address of the authorisation holder | Chanelle Medical, Loughrea, Co. Galway, Ireland. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Montelukast sodium
Chemical name: \([\text{R-(E)}]-1-[[[1-3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.\]

Structural formula:

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 (Pearlitol 50C), hydroxypropyl cellulose (Klucel LF), sodium laurilsulfate and magnesium stearate.
All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

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

**Pharmaceutical Development**

The objective of the development programme was to formulate immediate-release granules containing 4 mg montelukast that could be considered as a generic medicinal product of Singulair 4 mg Granules (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 product, 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**

The finished product is packaged in Claycoated kraft/low density polyethylene/aluminium/Surlyn sachets and is available in pack sizes of 7, 20, 28 and 30 sachets.

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 finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with the storage conditions ‘Store in the original package in order to protect from light and moisture’.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA Forms
The MAA form is satisfactory.

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

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

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of montelukast sodium are well-known, no new non-clinical studies are required and none have been provided.

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

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

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

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, single-dose, two-treatment, two-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Montelukast 4 mg granules versus the reference product Singulair 4mg Granules (Merck Sharp & Dohme BV, Netherlands) in healthy adult volunteers under fasted conditions.
All volunteers received a single oral dose of either the test or reference product administered by sprinkling on the tongue without water after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for montelukast are presented below (non-transformed values; arithmetic mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml/h</th>
<th>AUC_{0-\infty} ng/ml/h</th>
<th>C_{max} ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>1180.17</td>
<td>1230.90</td>
<td>200.76</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>1226.05</td>
<td>1283.41</td>
<td>190.50</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>(97.60 (92.02-103.52%)</td>
<td>(97.28 (91.70-103.18%)</td>
<td>(107.88 (100.74-115.53%)</td>
</tr>
</tbody>
</table>

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

*ln-transformed values

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

**Pharmacodynamics**

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

**Efficacy**

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

**Safety**

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

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

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

**Clinical Expert Report**

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

**Pharmacovigilance System and Risk Management Plan**

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

A suitable justification has been provided for not submitting a Risk Management Plan for this product.
Conclusion
There are no objections to the approval of this application from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Montelukast 4 mg granules 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 4 mg granules and its respective reference product (Singulair 4mg Granules).

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

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

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with montelukast sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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