OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Montelukast SVUS

4 mg, 5 mg chewable tablets,
10 mg film-coated tablets

(montelukast)

Procedure number: HU/H/0483/001-003/DC

Marketing authorisation holder: SVUS Pharma a.s.

Date: 20 May 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Montelukast SVUS 4 mg, 5 mg chewable tablets, 10 mg film-coated tablets (named Montelukast Farmax in Czech Republic and Poland). The holder of the marketing authorisation is SVUS Pharma a.s. in the Reference Member State.

The active substance is montelukast.

Each chewable tablet contains montelukast sodium which corresponds to 4 mg or 5 mg of montelukast. Each film-coated tablet contains montelukast sodium which corresponds to 10 mg of montelukast.

The other ingredients are:
- chewing tablets: mannitol, spray dried (E421), cellulose, microcrystalline, aspartame (E951). low-substituted hydroxypropyl cellulose, iron oxide red (E 172), croscarmellose sodium, cherry flavour (consisting of flavouring substances, arabic gum E414, maltodextrin, propylene glycol E1520) and magnesium stearate;
- film-coated tablets:
    - tablet core: mannitol, spray dried (E421), cellulose, microcrystalline, low-substituted hydroxypropyl cellulose, croscarmellose sodium, banana flavour (consisting of flavouring substances, maltodextrin, modified starch E1450 and propylene glycol E1520), aspartame (E951) and magnesium stearate,
    - coating: hypromellose 3cP, hydroxypropylcellulose, talc, titanium dioxide (E 171), iron oxide yellow (E 172) and iron oxide red (E 172).

The 4 mg chewable tablets are pink, flat round, with bevelled edges, marked with ‘4’ on one side and plain on the other, with a nominal diameter of 7 mm.

The 5 mg chewable tablets are pink, flat round, with bevelled edges, with a nominal diameter of 7 mm.

The film-coated tablets are beige, round, biconvex, with a nominal diameter of 8 mm.

Both the chewable and film-coated tablets are available in packages in OPA/Al/PVC//Al blisters.

The active principle of Montelukast SVUS (further on: Montelukast) chewable tablets and film-coated tablets is a leukotriene receptor antagonist that blocks substances called leukotrienes.

Leukotrienes cause narrowing and swelling of airways in the lungs. By blocking leukotrienes, these medicinal products improve asthma symptoms and helps control asthma.

Leukotirenes also cause allergy symptoms. Using Montelukast 10 mg film-coated tablets also improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

The doctor prescribes Montelukast chewable tablets to treat a child's asthma, preventing asthma symptoms during the day and night.

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

The doctor will determine how Montelukast chewable tablets should be used depending on the symptoms and severity of the child's asthma.

The doctor has prescribes Montelukast film-coated tablets to treat asthma and preventing the asthma symptoms during the day and night.

- Montelukast film-coated tablets are used for the treatment of adults and adolescents 15 years of age and older who are not adequately controlled on their medication and need additional therapy.
- Montelukast film-coated tablets also help prevent the narrowing of airways triggered by exercise.
- In those asthmatic patients in whom Montelukast film-coated tablets are indicated in asthma, they can also provide symptomatic relief of seasonal allergic rhinitis.

The doctor will determine how Montelukast film-coated tablets should be used depending on the symptoms and severity of the 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.

What are seasonal allergies? Seasonal allergies (also known as hay fever or seasonal allergic rhinitis) are an allergic response often caused by airborne pollens from trees, grasses and weeds. The symptoms of seasonal allergies typically may include stuffy, runny, itchy nose; sneezing; watery, swollen, red, itchy eyes.

What patints or patients' parents need to know before taking Montelukast film-coated tablets or giving the child Montelukast chewable tablets

The doctor should be informed about any medical problems or allergies the patient has now or has had.

Those who are allergic to montelukast or any of the other ingredients of this medicine, *should not take it*.

Warnings and precautions

Consult the doctor before taking Montelukast film-coated tablets or give Montelukast chewable tablets to a child.

- If the patient's asthma or breathing gets worse, th doctor must be told immediately.
- Oral montelukast is not meant to treat acute asthma attacks. If an attack occurs, instructions the doctor has given must be followed. The patient's (or the child-patient's parent) must always have his/her/the child's inhaled rescue medicine for asthma attacks with him/her.
- It is important that the patient take all asthma medications prescribed by the doctor. Montelukast film-coated or chewable tablets should not be used instead of other asthma medications the doctor has prescribed.
- Any patient (patient's parent if the child is) on anti-asthma medicines, should 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, the doctor should be consulted.
- Patients, including children should not take acetyl-salicylic acid, or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make their asthma worse.

Children and adolescents

Montelukast chewable tablets must not be given to children less than 2 years of age.

Montelukast film-coated tablets must not be given to children less than 15 years of age.

There are different form(s) of this medicine available for paediatric patients under 18 years of age based on age range.

Other medicines and Montelukast chewable or film-coated tablets

If the patient (child) is taking or has recently been taken/given or might take/be given any other medicines including those obtained without a prescription, the doctor should be consulted.

Some medicines may affect how montelukast works, or montelukast may affect how other medicines work, particularly

- phenobarbital (used for treatment of epilepsy),
- phenytoin (used for treatment of epilepsy),
- rifampicin (used to treat tuberculosis and some other infections),

- (in case of adult patients also) gemfibrozil (used for treatment of high lipid levels in plasma).

Montelukast chewable and film-coated tablets with food and drink

Montelukast chewable tablets should not be taken immediately with food; they should be taken at least 1 hour before or 2 hours after food.

Montelukast film-coated tablet may be taken with or without food.

Pregnancy and breast-feeding

This subsection is not applicable for the Montelukast chewable tablets since they are intended for use in children 2 to 5 years of age.

As for Montelikast tablets, those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking them.

Pregnancy: the doctor will assess whether the patient can take Montelukast film-coated tablets during this time.

Breast-feeding: it is not known if montelukast appears in breast milk. Those who are breast-feeding or intend to breast-feed should consult their doctor.

Driving and using machines

This subsection is not applicable for the Montelukast chewable tablets since they are intended for use in children 2 to 5 years of age.

Montelukast film-coated tablets are not expected to affect the ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported with montelukast may affect some patients' ability to drive or operate machinery.

*Montelukast chewable and film-coated tablets contain aspartame***,** a source of phenylalanine. May be harmful for people with phenylketonuria.

How to take Montelukast chewable and film-coated tablets

This medicine should always be taken exactly as the doctor or pharmacist has prescribed.

Montelukast chewable tablets

- This medicine is to be given to a child under adult supervision. For children who have problems consuming a chewable tablet, an oral granule formulation is available.

- The child should take only one chewable tablet once a day as prescribed by the doctor.
- It should be taken even when the child has no symptoms or if he/she has an acute asthma attack.

Montelukast film-coated tablets

- The patient should take only one tablet once a day as prescribed by the doctor.
- It should be taken even when the patient has no symptoms or have an acute asthma attack.

These medicines are for oral use.

For children 2 to 5 years of age: the recommended dose is one Montelukast chewable tablet daily to be taken in the evening. If the child is taking Montelukast chewable tablet, the parents should be sure that he/she does not take any other medicines that contain the same active ingredient, montelukast. The tablets are to be chewed before swallowing. Montelukast chewable tablets should not be taken immediately with food; it should be taken at least 1 hour before or 2 hours after food.

For adults and adolescents 15 years of age and older: the recommended dose is one Montelukast 10 mg film-coated tablet to be taken daily in the evening.
Patients who are taking Montelukast film-coated tablets should be sure that they do not take any other products that contain the same active ingredient, montelukast. The tablet can be taken with or without food.

What to do if the patient takes more Montelukast chewable or film-coated tablets than he/she should?

The doctor must be contacted 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.

What to do if taking Montelukast film-coated tablets (giving to the child Montelukast chewable tablets) has been forgotten?

Patients/parents should try to take/give Montelukast film-coated /chewable tablets as prescribed. However, if the patient/the child misses a dose, just resume the usual schedule of one chewable tablet once daily. No double dose should be taken to make up for a forgotten dose.

May the patient/child stop taking Montelukast film-coated/chewable tablets?

These medicinal products can treat the asthma only the patient/child continues taking it. It is important for to continue taking Montelukast film-coated or chewable tablets for as long as the doctor prescribes. It will help controlling the asthma.

Possible side effects

Like all medicines, these medicines can cause side effects, although not everybody experiences them.

In clinical studies with montelukast film-coated tablets and chewable tablets, 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:

- abdominal pain,
- thirst (only for 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).

Additionally, while the medicine has been on the market, the following have been reported (the frequency of possible side effects listed below is defined using the following convention).

Very common (may affect more than 1 in 10 people): upper respiratory infection,

Common (may affect up to 1 in 10 people):
- diarrhoea, nausea, vomiting,
- rash,
- fever.

Uncommon (may affect up to 1 in 100 people)
- allergic reactions including swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing,
- behaviour and mood related changes such as dream abnormalities, including nightmares, trouble sleeping, sleep walking, irritability, feeling anxious, restlessness, agitation including aggressive behaviour or hostility, depression,
- dizziness, drowsiness, pins and needles/numbness, seizure,
- nosebleed,
- dry mouth, indigestion,
- bruising, itching, hives,
- joint or muscle pain, muscle cramps,
- weakness/tiredness, feeling unwell, swelling.

Rare (may affect up to 1 in 1,000 people)
- increased bleeding tendency,
- tremor, disturbance in attention, memory impairment,
- palpitations.

Very rare (may affect up to 1 in 10,000 people)
- hallucinations, disorientation, suicidal ideas and actions,
- swelling (inflammation) of the lungs,
- hepatitis (inflammation of the liver),
- tender red lumps under the skin most commonly on your shins (erythema nodosum), severe skin reactions (erythema multiforme) that may occur without warning.

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. If a patient (child) gets one or more of these symptoms, the doctor must be informed right away.

How to store Montelukast chewable tablets and film-coated tablets

This medicinal product does not require any special temperature storage condition. It should be stored in the original packaging in order to protect from light and should be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Montelukast SVUS 4 mg, 5 mg chewable tablets and 10 mg film-coated tablets. The procedure was finalised at 13 September 2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance with the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Czech Republic, Poland Slovak Republic) concerned the generic version of montelukast 4 mg, 5 mg chewable tablets and 10 mg film-coated tablets, respectively (Montelukast SVUS tablets, named Montelukast Farmax in the Czech Republic and Poland).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new non-clinical or clinical data, other than supporting literature where necessary. The applicant has adequately demonstrated bioequivalence between the 5 mg chewable tablets, 10 mg film-coated tablets and the reference products. The applicant claimed for biowaiver for the dose strength of 4 mg chewable tablets.

The reference products were Singulair 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets (Merck Sharpe and Dohme). The 10 mg film-coated tablets and 5 mg chewable tablets were authorised in the RMS in 1998, the 4 mg chewable tablets in 2002.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Montelukast SVUS 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets (SVUS Pharma a.s.).

The products are indicated for 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 β-agonists provide inadequate clinical control of asthma and in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

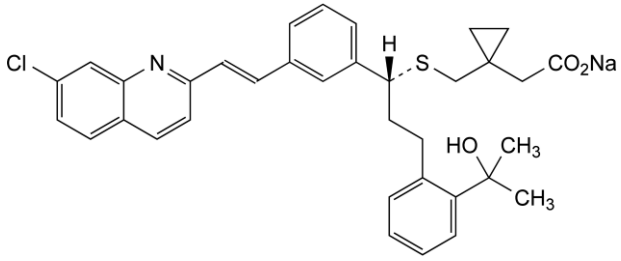
This chemical-pharmaceutical assessment report concerns the application of Montelukast 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

The reference products are Singulair® 4 mg and 5 mg, chewable tablets and Singulair® 10 mg film-coated tablets (containing montelukast sodium as active ingredient) from Merck Sharpe and Dohme.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using two European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: montelukast
Chemical name: sodium [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)-ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-propyl]sulfanyl]methyl]cyclopropyl]acetate
Structure:



The drug substance is white or almost white, hygroscopic powder, freely soluble in water and in methylene chloride, freely soluble to very soluble in ethanol (96 per cent). Both manufacturers consistently produce the amorphous form and the correct isomer.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents and particle size distribution. The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council of Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturers and the drug product manufacturer for the control of the substance are adequately characterised.

The drug substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods, and demonstrate the batch to batch consistency of the production.

A retest period and the packaging material have been mentioned on the CEPs or it has been stated that the drug substance will be tested by the drug product manufacturer immediately prior to use.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

II.3.1 Chewable tablets

The aim was to develop a stable formulation of montelukast 4 mg and 5 mg chewable tablets, pharmaceutically equivalent to the innovator and reference products Singulair® by Merck Sharp & Dohme.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.

4 mg: pink, flat round, chewable tablets with bevelled edges, marked with ‘4’ on one side and plain on the other, with a nominal diameter of 7 mm.
5 mg: pink, flat round, chewable tablets with beveled edges and a nominal diameter of 8 mm.

The excipients used in the finished product are iron oxide red (E172), cherry flavour, aspartame, magnesium stearate, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium and mannitol. All excipients used comply with their respective Ph. Eur. monograph, except for cherry flavour. (The components of

cherry flavour comply with Food Chemical Codex.) Compliance of the product with the general monograph of the Ph. Eur. *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following storage restriction: “Store in the original packaging in order to protect from light. This medicinal product does not require any special temperature storage condition”.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.3.2 Film-coated tablets

The aim of the development was to develop a stable formulation of montelukast 10 mg film-coated tablets, pharmaceutically equivalent to the reference and innovator product Singulair® by Merck Sharp & Dohme.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained: beige, round, biconvex, film-coated tablets with a nominal diameter of 8 mm.

The excipients used in the finished product are banana flavour, aspartame, magnesium stearate, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium, mannitol and Opadry yellow (red and yellow iron-oxide, titanium dioxide, talc, hypromellose and hydroxypropylcellulose). All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following storage restriction: “Store in the original packaging in order to protect from light. This medicinal product does not require any special temperature storage condition”.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Montelukast SVUS 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of montelukast are well known. As montelukast is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The non-clinical overview is therefore based on up-to-date and adequate scientific literature.

III.2 Pharmacology

Montelukast is a leukotriene-receptor antagonist, it has anti-inflammatory and bronchodilatator effects.

III.3 Pharmacokinetics

Montelukast is rapidly absorbed. More than 99% is bound to plasma proteins with minimal distribution across the blood-brain barrier. Metabolism occurs via liver P450 (CYP) 3A4 and 2CP microsomes, with potent inhibition of P450 2C8. Excretion occurs almost exclusively in bile. The pharmacokinetic profile is similar in females and males, young and elderly.

III.4 Toxicology

In animal toxicology studies, minor serum biochemical alterations in alanin-aminotransferase, glucose, phosphor and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal 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 dosage). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure 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 neither mutagenic in *in vitro* and *in vivo* tests, nor tumorigenic in rodent species.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Montelukast SVUS 4 mg and 5 mg chewable tablets and Montelukast SVUS 10 mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics, and toxicology of montelukast are well-known.

Abridged applications avoid the need for repetitive tests on animals. As these products are generic formulations of Singulair 4 mg and 5 mg chewable tablets and Singulair 10 mg film-coated tablets, there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Montelukast is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided which is based on scientific literature. Except for showing bioequivalence, no specific clinical studies have been performed and no further clinical studies are required.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Montelukast is absorbed from the gastro-intestinal tract after oral administration with a mean time to peak serum concentration of approx. 3 hours. Mean bioavailability with the 10 mg film-coated tablet is 60–70%. Food does not impair the absorption of montelukast to a clinically significant extent.

Montelukast is extensively metabolised. Major metabolic pathways include acyl glucuronidation (M1), sulfoxidation (M2), hydroxylation of the isopropylphenyl moiety (M3), further oxidation of the 36-OH metabolite (M6) to a dicarboxylic acid (M4) and hydroxylation at the 21-position (M5). Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally, CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily.

Excretion is primarily via faeces and bile with only low levels of metabolites observed in plasma.

IV.2.2 Bioequivalence studies

The applicant submitted two pivotal bioequivalence studies in order to support essential similarity between:

- Montelukast SVUS 5 mg chewable tablets and Singulair® 5 mg chewable tablets (manufactured by Merck Sharp & Dohme Ltd., UK),
- Montelukast SVUS 10 mg tablets and Singulair® 10 mg tablets (manufactured by Merck Sharp & Dohme Ltd., UK)

in healthy adult male volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

By the sponsor's statement the bioequivalence studies were conducted in compliance with the requirements of guideline on *Good Clinical Practice" ICH Topic E6 (R1)* (*CPMP/ICH/135/95*) and ethical principles stated in the last revision of Declaration of Helsinki.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study with the 5 mg chewable tablets

It was a pivotal, single-dose, randomized, open-label, crossover study of montelukast Test and Reference chewable tablets.

Healthy adult subjects were administered the Test- and Reference medications (as per the randomisation scheme) as a single oral dose of one chewable tablet of Test (5 mg montelukast) and 1 chewable tablet of Reference products (5 mg montelukast) without water. in each study period under fasting conditions. Subjects were asked to slowly and thoroughly chew the tablet.

The results are shown in the Table below.

Pharmacokinetic parameter	Ratio (Test/Reference)
AUC_{0-t}	94.09
$AUC_{0-\infty}$	94.04
C_{max}	92.19

No death or serious adverse events occurred during the study. All adverse events were mild in severity and resolved. Overall, the drugs investigated were well tolerated by subjects included in the study.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 4 mg chewable tablets on the basis of general biowaiver requirements *(CPMP/EWP/QWP/1401/98 Rev 1 Corr**):*

a. Both strengths i.e. 4mg and 5 mg of proposed pharmaceutical products (chewable tablets) are manufactured by the same manufacturer and using the same manufacturing process.
b. The qualitative composition of the different strengths is the same.
c. The compositions of the claimed two strengths (4 and 5 mg) are proportionally similar.

d. *In-vitro* dissolution data confirm the *in vivo* similarity between the claimed strengths.
e. Montelukast exhibits linear pharmacokinetics in the therapeutic range of 4-10 mg.

Bioequivalence study with the 10 mg film-coated tablets

It was a pivotal, single-dose, randomized, open-label, crossover, bioequivalence study of montelukast 10 mg film-coated tablets in healthy adult subjects under fasting condition.

The subjects were administered the Test- and Reference medications (as per the randomisation scheme) as a single oral dose of 1 tablet of Test (10 mg montelukast) and 1 tablet of Reference products (10 mg montelukast) with room temperature water.

The results are shown in the Table below.

Pharmacokinetic parameter	Ratio (Test/Reference)
AUC_{0-t}	91.88
$AUC_{0-\infty}$	91.87
C_{max}	89.23

No death or serious adverse events occurred during the study. The adverse events were mild in severity and resolved.

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Montelukast SVUS 10 mg film-coated tablets and 5 mg chewable tablets are considered bioequivalent with Singulair® 10 mg film coated tablets and 5 mg chewable tablets. The results of the bioequivalence study with the 5 mg chewable tablet formulation can be extrapolated to the lower dose strength of montelukast 4 mg, since all conditions according to the relevant guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) were fulfilled.

IV.3 Pharmacodynamics

Montelukast is an oral cysteinyl leukotriene D4 receptor antagonist.

IV.4 Clinical efficacy

Apart from the two bioequivalence studies, no further efficacy studies were submitted, which is acceptable as this is a generic application.

IV.5 Clinical safety

During the submitted bioequivalence studies, no new, unexpected adverse events were reported. Bioequivalence between the Test and Reference products was demonstrated, so their clinical safety is also considered equivalent.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the Good Pharmacovigilance Practice module, the RMS considers the Summary acceptable.

IV.6.2 Risk Management Plan

The applicant has submitted an updated risk management plan in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Montelukast SVUS 4 mg and 5 mg chewable tablets and Montelukast SVUS 10 mg film-coated tablets

The applicant has identified the following safety concerns.

Summary of safety concerns	
Important identified risks	Upper respiratory infection. Increased bleeding tendency. Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury). Erythema nodosum, erythema multiforme. Hypersensitivity reaction including anaphylaxis.
Important potential risks	Suicidal thinking, behaviour (suicidality) and depression. Systemic eosinophilia, sometimes with clinical features of vasculities consistent with Churg-Strauss syndrome.
Missing information	Use in children under 2 years of age. Use in pregnancy. Use in lactation.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all safety concerns connected to to Montelukast SVUS 4 mg and 5 mg chewable tablets and Montelukast SVUS 10 mg film-coated tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Montelukast SVUS 4 mg and 5 mg chewable tablets and Montelukast SVUS 10 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

With regard to Periodic Safet Report (PSUR) submission, the markting authorisation holder should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the data lock point (DLP) and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on humans. For these applications the bioequivalence studies described in section IV.2 are pivotal.

In this application, reference is made to the clinical studies and experience with the reference product Singulair. No new clinical studies were conducted. The applicant demonstrated through two bioequivalence studies that the pharmacokinetic profile of the Montelukast 10 mg tablets and Montelukast 5 mg chewable tablets is similar to the pharmacokinetic profile of the reference products. The biowaiver claim for the 4 mg chewable tablet formulation can be accepted.

The clinical part of the application is acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Montelukast SVUS 4 mg and 5 mg chewable tablets, as well as Montelukast SVUS 10 mg film-coated tablets, generic versions of montelukast. The applicant and the future holder of authorisation is SVUS Pharma a.s.

The products are indicated for 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 β-agonists provide inadequate clinical control of asthma and in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Singulair® 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets (Merck Sharp & Dohme Ltd.). To support the application the applicant demonstrated bioequivalence between the Test and Reference 5 mg chewable tablets as well as between the 10 mg film-coated tablets. The biowaiver claim for the 4 mg chewable tablets was adequately justified.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Montelukast SVUS 4 mg and 5 mg chewable tablets, and Montelukast SVUS 10 mg film-coated tablets

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Transfer of marketing authorisation to Neuraxpharm Bohemia s.r.o. in the RMS		yes		16. 11. 2018	approval	no
Withdrawal of the marketing authorisation of the 4 mg chewable tablets in the RMS, initiated by the marketing authorisation holder		yes		22. 10. 2019	approval	no
Withdrawal of the marketing authorisation of the 4 mg chewable tablets in the CMSs, initiated by the marketing authorisation holder						