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MONTELUKAST 10 MG FILM-COATED TABLETS

Montelukast sodium

PL 24668/0236-7

LAY SUMMARY

On 25th October 2012, the MHRA granted Caduceus Pharma Ltd Marketing Authorisations (licences) for the medicinal products Montelukast 10 mg Film-coated Tablets (PL 24668/0236-7). These medicines are only available on prescription from a doctor.

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

Montelukast is prescribed to treat asthma, preventing your asthma symptoms during the day and night.

• Montelukast is used for the treatment of patients who are not adequately controlled on their medication and need additional therapy.
• Montelukast also helps prevent the narrowing of airways triggered by exercise.
• In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

The use of Montelukast is determined by your doctor depending on the symptoms and severity of your 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.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Montelukast 10 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
MONTELUKAST 10 MG FILM-COATED TABLETS

Montelukast sodium

PL 24668/0236-7

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations (licenses) for the medicinal products Montelukast 10 mg Film-coated Tablets (PL 24668/0236-7) on 25th October 2012. These are duplicate applications used in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

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

These duplicate national abridged applications for Montelukast 10 mg Film-coated Tablets are submitted under Article 10(1) of Directive 2001/83/EC, as amended. These products are cross-referring to Singulair 10 mg Film-coated Tablets (PL 00025/0358), authorised on 15th January 1998 to Merck Sharp & Dohme Limited.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT₁ receptor.

The cysteinyi leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyi leukotriene (CysLT) receptors. The CysLT type-1 (CysLT₁) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

A pharmacovigilance system has been provided with these applications and is satisfactory.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Montelukast Sodium


[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

Structure:

![Structure Image]

Molecular Formula: C_{35}H_{35}ClN_{2}NaO_{3}S
Molecular Weight: 608.18
Appearance: White to off-white crystalline powder.

The drug substance is the subject of a European Drug Master File (EDMF). Letter of access have been provided by the drug substance manufacturers.

Synthesis of the drug substance from the designated starting material 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 drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided, which comply with the proposed specification.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

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

**DRUG PRODUCT**

Other ingredients

Other ingredients consist of the pharmaceutical excipients cellulose, microcrystalline, hydroxypropylcellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate making up the tablet core; and the film-coat is consisted of lactose monohydrate, hypromellose 15cP, titanium dioxide, macrogol 4000, iron oxide yellow (E172) and iron oxide red (E172).

All excipients comply with their respective European Pharmacopoeia monograph with the exception of iron oxide yellow (E172) and iron oxide red (E172) which comply with United States national formulae. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin are lactose monohydrate and magnesium stearate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical development**

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited).

Comparable dissolution and impurity profile are provided for these products versus the originator product.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches.
Finished product specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Container Closure System
The tablets are packed in aluminium/aluminium blister. Each blister strip contains 7, 10, 14, 20, 28, 49, 50, 56, 84, 90, 98, 100, 140 and 200 tablets

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with relevant EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with storage conditions “Store in the original package in order to protect from light and moisture” and “Do not store above 30°C” are set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labels are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report/Quality overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of montelukast sodium are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

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

There are no objections to the approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study comparing Montelukast 10 mg Film-coated Tablets (Actavis Group PTC ehf, Iceland) with Singulair® (Montelukast Sodium) 10 mg Film-coated Tablets (MSD Dieckmann Anneimittel GMBH, Germany) in healthy adult subjects, under fasting conditions.

Blood samples were collected within 1 hour before dosing and at 0.5, 1.0, 1.333, 1.667, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 12.0, 16.0 and 24.0 hours post-dose under yellow monochromatic light. There was a washout period of 7 days between dosing.

Results

<table>
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<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio</th>
<th>90% Confidence Interval</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 90% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper 90% CI</td>
</tr>
<tr>
<td>AUC₀⁻ₜ</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>AUC₀⁻∞</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>Cₘₐₓ</td>
<td>1.08</td>
<td>0.96</td>
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</table>

The 90% confidence intervals for AUC and Cₘₐₓ were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Montelukast 10 mg Film-coated Tablets) and the reference formulation (Singulair® 10 mg Film-coated Tablets).

EFFICACY

No new efficacy data have been submitted and none are required for these applications.

SAFETY

No new safety data have been submitted and none are required for these applications.

EXPERT REPORT/Clinical Overall Summary

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS

These are satisfactory.

PATIENT INFORMATION LEAFLET

This is satisfactory.
LABELLING
This is satisfactory.

MAA FORMS
These are satisfactory.

CONCLUSIONS
There are no objections to the approval of these products from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Montelukast 10 mg Film-coated Tablets and the reference formulation (Singulair® 10 mg Film-coated Tablets).

No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has also been submitted.

RISK BENEFIT 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 risk benefit is, therefore, considered to be positive.
MONTELUKAST 10 MG FILM-COATED TABLETS

Montelukast sodium

PL 24668/0236-7

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<th>STEPS TAKEN FOR ASSESSMENT</th>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 6th March 2009</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 19th March 2009</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 28th June 2011 and on the clinical section 21st August 2009 and 3rd June 2010</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 27th February 2012 and on the clinical section on 25th February 2010 and 29th July 2010</td>
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<tr>
<td>5</td>
<td>The applications were determined on 25th October 2012.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING