Decentralised Procedure

Public Assessment Report

Montelukast 1 A Pharma 10 mg Filmtabletten

Montelukast

DE/H/5912/001/DC

(formerly UK/H/2201/001/DC)

Applicant: 1 A Pharma GmbH

Date: 10.02.2020

This module reflects the scientific discussion for the approval of “Montelukast 1 A Pharma 10 mg Filmtabletten”. The procedure was finalised on 4th November 2009.
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<td><strong>Concerned Member States:</strong> DK, PL, PT</td>
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| **Applicant (name and address):** 1 A Pharma GmbH  
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I. INTRODUCTION
On 4th November 2009, Denmark, Germany, Poland, Portugal and the UK agreed to grant a marketing authorisation to Sandoz Limited for the medicinal product Montelukast 10mg Film-Coated Tablets. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS – UK/H/2201/001/DC). After the national phase, a licence was granted in the UK on 20th November 2009 (PL 33118/0001).
This application was made under Article 10.1 of Directive 2001/83 EC for Montelukast 10mg Film-Coated Tablets, containing the known active substance montelukast sodium. The reference medicinal product for this application is Singulair 10mg Tablets (Merck, Sharp and Dohme), which has been licenced in at least one member state for over 10 years.
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. Monelukast is also indicated in prophylaxis of exercise-induced bronchoconstriction and symptomatic relief of seasonal allergic rhinitis.
The drug product corresponds to the current EU definition for generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, and the same dosage form.
The bioequivalence study was conducted in accordance with current Good Clinical Practice.
A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.
An acceptable justification for not submitting a European Risk Management Plan has been provided.
Other documentation relating to pharmacovigilance system have been provided.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

After changing the RMS, Germany is the new RMS. The former procedure number was UK/H/2201/001/DC.

II. QUALITY ASPECTS
II.1 Drug substance
INN name: Montelukast sodium
Chemical name: Sodium salt of 1-[[[(1R)-1-[(3-[(1E)-2(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid

Structure:
Molecular formula: $C_{35}H_{35}ClNO_{3}SNa$
Molecular weight: 608.18
Physical form: A white to almost white powder, soluble in water, methanol and ethanol, and practically insoluble in acetonitrile.

Montelukast exhibits chirality and polymorphism.
Synthesis of the drug 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. No materials of animal or human origin are used in the production of the active substance.

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. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food. Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

II.2 Drug Product

Other ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, hydroxypropylcellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified water and Opadry beige (which consisted of hypromellose, titanium dioxide, macrogol, yellow ferric oxide and red ferric oxide). All excipients are controlled to their respective European Pharmacopoeia monograph, with the exception of red ferric oxide and yellow ferric oxide, which are controlled to suitable French National Formulary specifications. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the originator product.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is supplied in oriented polyamide/aluminium/polyvinylchloride blisters in pack sizes of 7, 10, 14, 20, 21, 28, 30, 49, 50, 56, 84, 90, 98, 100, 140 and 200 tablets. Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in 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 2 years has been set, with the storage instructions “Do not store above 30°C. Store in the original package in order to protect from moisture and light”.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory. The marketing authorisation holder has committed to submitting mock-ups of the patient information leaflet and labels to the relevant regulatory authorities before marketing the product in any member state.
The applicant has submitted results of PIL user testing. The results indicate that the PIL 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.

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

**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.

### III. NON-CLINICAL ASPECTS
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.

**Environmental Risk Assessment (ERA)**
There is no environmental risk assessment statement included in the application. This is acceptable for a generic product.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
The SPC is satisfactory from a preclinical viewpoint.

**NON-CLINICAL EXPERT REPORT**
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

**OVERALL CONCLUSION ON THE NON-CLINICAL PART**
The applicant has provided an adequate review of the available non-clinical data. The pattern of toxicity seen with irinotecan is consistent with its anti-cancer actions. There were no new non-clinical data identified in the literature review that would change the risk-benefit analysis for irinotecan.

### IV. CLINICAL ASPECTS

**Pharmacokinetics**
With the exception of the bioequivalence study, no new data have been submitted and none are required for an application of this type. The bioequivalence study was conducted in line with Good Clinical Practice and the Declaration of Helsinki.

**Bioequivalence**
A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Montelukast 10mg Film-Coated Tablets (test) versus Singulair 10mg Tablets (reference) in healthy fasted subjects.
A single dose of test or reference study drug was administered with 240ml of water after an overnight fast of at least 10 hours. Blood samples were taken pre- and up to 24 hours post dose. Each treatment arm was separated by a 7-day washout period.

**Results**
The pharmacokinetic results for active montelukast sodium are presented below:
Conclusions
The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
Montelukast sodium has an acceptable adverse events profile. No new safety concerns arise from the bioequivalence study and the safety profiles of this product and the reference product (Singulair 10mg Tablets) are similar.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

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

MAA Form
The MAA Form is medically satisfactory.

Clinical Conclusion
The grant of a Marketing Authorisation is recommended.
V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Montelukast 10mg 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.

PRECLINICAL
The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Montelukast 10mg Film-Coated Tablets beyond those already described.

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

Montelukast 10mg Film-Coated Tablets is the generic version of Singulair 10mg Tablets (Merck, Sharp and Dohme). The use of the reference product is well-established in the UK.

Both products contain the same quantitative and qualitative composition of the active ingredient, irinotecan hydrochloride trihydrate.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Montelukast sodium has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator 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.

The application is approved. For intermediate amendments see current product information.