Public Assessment Report

Scientific discussion

Tevalukast
Chewable tablets 4 mg and 5 mg

Montelukast sodium

DK/H/1331/001-002/DC

This module reflects the scientific discussion for the approval of Tevalukast. The procedure was finalised on 24 September 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tevalukast 4 mg and 5 mg chewable tablets, from Teva Denmark A/S. The date of authorisation was on 18 December 2008 in Denmark.

Tevalukast 4 mg chewable tablets is indicated for the treatment of asthma as add-on therapy in those 2 to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma. Tevalukast 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. Tevalukast is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

Tevalukast 5 mg chewable tablets is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma. Tevalukast may also be an alternative treatment option to low-dose inhaled corticosteroids for patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids. Tevalukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Montelukast is used as an anti-asthmatic for systemic use.

Montelukast is an orally active compound which binds with high affinity and selectively to the $CysLT_1$ receptor. The cysteinyl leukotrienes (LTC_4 , LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-ashmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. Bronchodilation was observed within 2 hours of oral administration.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Singulair chewable tablets 4 mg and 5 mg which has been authorised in the RMS since 16 January 2001 (4 mg) and 20 January 1998 (5 mg).

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Tevalukast 4 mg and 5 mg chewable tablets contain as active substance montelukast sodium, which is equivalent to 4 mg and 5 mg montelukast, respectively.

The 4 mg tablets are mottled pink, arc triangle shaped tablets, debossed with "93" on one side and "7424" on the other side of the tablet.
The 5 mg tablets are mottled pink, square shaped tablets, debossed with "93" on one side and "7425" on the other side of the tablet.

Tevalukast chewable tablets are packed in aluminium-aluminium blister packs. Packs of 7, 14, 15, 20, 28, 30, 50, 56, 60, 90, 98 and 100 tablets have been approved. However, not all pack sizes may be marketed.

The excipients in the tablets are: Mannitol (E421), sodium laurilsulfate, hydroxypropyl cellulose, red iron oxide (E172), flavour.cherry PHS-143671, maltodextrins (maize) and starch modified E1450 (Waxy maize), aspartame (E951), sodium starch glycolate (maize) Type A and magnesium stearate.

Compliance wih Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP are in place for his product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, montelukast sodium, is in compliance with the present European regulatory requirements.

The Active Substance Master File (ASMF) procedure is used for the active substance.

The control tests and specifications for the drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.
A re-test period/storage condition of 24 months is accepted when stored in double LDPE bags inside double triple laminated bags, all purged with nitrogen and containing silica gel bags.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results were provided for 2 batches of the 5 mg strength and 3 batches of the 4 mg strength. The batch analysis results show that the finished products meet the specifications proposed.

The active substance is optically active. The enantiomeric purity is adequately controlled in the active substance. It has been made probable that no significant change in stereochemical purity occurs during manufacture and storage of the product. However, the matter will be followed during the stability studies.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

Samples from 3 pilot batches of 4 mg and 2 pilot batches of 5 mg were taken at pre-determined times. Results of 24 months at 25°C/60%RH (long term study), 12 months at 30°C/65%RH (intermediate conditions) and 6 months at 40°C/75%RH (accelerated conditions) were presented.
Since it was demonstrated during the stress testing that the product is sensitive to light, this should appear from the storage conditions.

Shelf life/storage conditions: 24 months/Do not store above 30°C/Keep blister in the outer carton in order to protect from light.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of montelukast are well known. This is a generic application and no new indications have been applied for. The applicant has not submitted new non-clinical information and an overview based on a literature review is therefore appropriate and acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Montelukast is a well-known active substance with established efficacy and tolerability

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Tevalukast 5 mg chewable tablets is compared with the pharmacokinetic profile of the reference product Singulair Paediatric 5 mg chewable tablets from the UK market.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The study was a single centre, open label, randomised, single dose, two-period, two-sequence, two-treatment, crossover study conducted under fasting conditions in 24 healthy volunteers (10 male and 14 female; 21-51 years; 48.3-94.8 kg; 15 x Caucasian, 6 x Asian, 3 x black) with a wash out period of 7 days between administrations. 5 mg was administered in each period by placing the tablet on the subject's tongue. The subjects then had to chew the tablet thoroughly and swallow, followed by a mouth check. Subjects were confined to the clinical research centre from at least 10 hours prior to drug administration until after the 24 hour post-dose blood draw in each period. Water was permitted ad lib until 1 hour before dosing and again 1 hour after dosing, otherwise *ad libitum*.

Blood sampling was performed predosing and at 0.33, 0.67, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16 and 24 hours post-dose in each period. 24 subjects were eligible for pharmacokinetic analysis.

Table 1

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test (S.D.)	1686.3 (612.4)	1744.6 (638.2)	264.5 (96.6)	1.67 (1.33-5.00)	4.80
Reference (S.D.)	1826.4 (564.0)	1880.2 (586.3)	288.8 (87.5)	2.67 (1.33-8.00)	4.46
***Ratio (90% CI)**	90.63% 85.84-95.69%	91.11% 86.49-95.97%	89.91% 82.69-97.75%	-	-
Intra-subject CV (%)	10.98%	10.52	17.00%	-	-

$AUC_{0-\infty}$ 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
T_{max} time for maximum concentration
$T_{1/2}$ half-life

**log-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of montelukast under fasted conditions, it can be concluded that Montelukast "Teva" 5 mg chewable tablets and Singulair Paediatric 5 mg chewable tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As Montelukast demonstrates linear pharmacokinetics, a single study using one tablet strength is appropriate for determining bioequivalence of the chewable tablets against reference.

The RMS has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice and Good Laboratory Practice.

IV.2 Risk management plan & Pharmacovigilance system

Montelukast was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of montelukast can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described 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 identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Singulair 4 mg and 5 mg chewable tablets.

Readability test

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 test consisted of two rounds with 10 participants. During the interviews the respondents were asked 14 questions and asked to answer in their own words. Prior to the test the package leaflet was pilot-tested.
The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Montelukast 4 mg and 5 mg chewable tablets have a proven chemical-pharmaceutical quality and is a generic form of Singulair chewable tablets. Singulair is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other montelukast containing products.

A European harmonised birth date has been allocated and subsequently the first data lock point for montelukast is 2009-07. The first PSUR should be submitted no later than 60 days after this date. A PSUR cycle of 3 years hereafter applies.

The date for the first renewal will be: 24 September 2013.

The following post-approval commitments have been made during the procedure:

- Process validation will be performed on the first 3 production scale batches (of each strength) manufactured at proposed manufacturing site(s).
  Certificates of analysis performed on the first 3 consecutive production scale batches (of each strength) will be forwarded when available.

- The enclosed stability studies will be continued.

- The first 3 production batches of each strength will be put on stability and tested according to the stability protocol as presented in section P.8.1.