Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Montelukast 10 mg film-coated tablets

(montelukast sodium)

PL 43870/0061

Medley Pharma Limited

LAY SUMMARY

Montelukast 10 mg film-coated tablets (montelukast sodium)

This is a summary of the Public Assessment Report (PAR) for Montelukast 10 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Montelukast Tablets in this lay summary for ease of reading

For practical information about using Montelukast Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Montelukast Tablets and what are they used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK), called Singulair 10 mg film-coated tablets.

Montelukast tablets are used to treat asthma, preventing asthma symptoms during the day and night.

Montelukast 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 Tablets also help prevent the narrowing of airways triggered by exercise.

In those asthmatic patients in whom Montelukast Tablets are indicated in asthma, Montelukast Tablets can also provide symptomatic relief of seasonal allergic rhinitis.

How do Montelukast Tablets work?
This medicine contains the active ingredient montelukast sodium, which is a leukotriene receptor antagonist. Leukotrienes cause narrowing and swelling of airways in the lungs and also cause allergy symptoms. By blocking leukotrienes, Montelukast Tablets improve asthma symptoms, help control asthma and improve seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

How are Montelukast Tablets used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is oral (by mouth).

The recommended dose for adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10 mg tablet daily to be taken in the evening.

For further information on how Montelukast Tablets are used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Montelukast Tablets have been shown in studies?
Because Montelukast Tablets are a generic medicine, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Montelukast Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Montelukast Tablets are a generic medicine, their benefits and possible side effects are considered to be the same as for the reference medicine.

Why were Montelukast Tablets approved?
It was concluded that, Montelukast Tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Montelukast Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Montelukast Tablets. The RMP details the important risks of Montelukast Tablets, how these risks can be minimised, any uncertainties about Montelukast Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

There is no safety concerns associated with the use of Montelukast Tablets.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Montelukast Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Montelukast Tablets

A marketing authorisation for Montelukast Tablets was granted in the United Kingdom (UK) on 11 September 2024.

The full PAR for Montelukast Tablets follows this summary.

This summary was last updated in October 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Montelukast 10 mg film-coated tablets (PL 43870/0061) could be approved.

The product is approved for the following indications:

- Montelukast 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. In those asthmatic patients in whom Montelukast is indicated in asthma, it 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

This product contains the active substance montelukast sodium, which is a leukotriene receptor antagonist that inhibits cysteinyl leukotriene (CysLT) receptors. 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 (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.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Singulair 10 mg film-coated tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Montelukast Tablets was granted in the United Kingdom (UK) on 11 September 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of film-coated tablets. Each film-coated tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

One film-coated tablet of Montelukast 10 mg Film-Coated Tablets contains montelukast sodium, which is equivalent to 10 mg of Montelukast.

In addition to montelukast, this product also contains the excipients mannitol, spray dried; cellulose, microcrystalline; low-substituted hydroxypropyl cellulose; croscarmellose sodium; banana flavor; aspartame; and magnesium stearate in the tablet core. The coating contains hypromellose 3cP; hydroxypropylcellulose; talc; titanium dioxide; iron oxide yellow (E 172); and iron oxide red (E 172).

The finished product is packaged in blisters of 7, 10, 14, 20, 28, 30, 50, 56 or 90 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

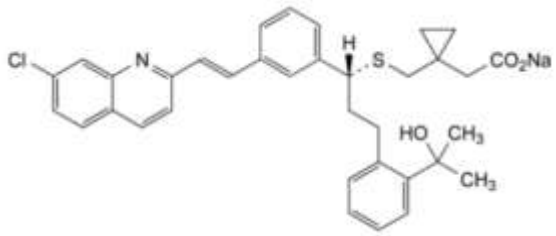
II.2 ACTIVE SUBSTANCE

rINN: Montelukast

Chemical Name: [1-[[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetate.

Molecular Formula: $C_{35}H_{36}ClNNO_3S$

Chemical Structure:



Molecular Weight:	608
Appearance:	White to almost white hygroscopic powder
Solubility:	Freely soluble in water and in methylene chloride, freely soluble to very soluble in ethanol (96 %)

Montelukast sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.
Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data 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 has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions ‘This medicinal product does not require any special temperature storage conditions; store in the original packaging to protect from light.’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
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. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of montelukast sodium is well-known. With the exception of data from a bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

Bioequivalence study (single-dose fasting conditions)
This was a randomised, open label, two- treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study comparing the test product Montelukast 10 mg film-coated tablets, versus the reference product, Singulair 10 mg Film-Coated Tablets, in adult, healthy, male and female human subjects, under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose of either of the test or reference product. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic data

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (ng*hr/mL)	2443.01 ± 729.45	2658.77 ± 905.89
$AUC_{(0-\infty)}$ (ng*hr/mL)	2530.64 ± 763.05	2754.69 ± 960.63
C_{max} (ng /mL)	395.63 ± 120.76	443.38 ± 152.80
t_{max} [3] (hrs)	3.50 (1.50-6.00)	3.00 (1.00-6.00)

[3] Median (Min, Max)

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
$AUC_{(0-t)}$	92.8862	86.8382-99.3554	21.52
C_{max}	90.1466	82.6266-98.3510	28.05

Geometric means and 90% confidence intervals

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-inf}	2411.35	2592.70	93.0052	87.0876	99.3249
AUC_{0-t}	2326.43	2504.61	92.8862	86.8382	99.3554
C_{max}	375.34	416.37	90.1466	82.6266	98.3510

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

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

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**