Saudi Public Assessment Report

Leukair ®

Active Pharmaceutical Ingredient(s): Montelukast

ATC code/CAS no.: R03D C03

Pharmaceutical/Dosage Form: Chewable Tablets

Dosage Strength: 4 mg - 5 mg

Marketing Authorization Holder: Saudi Pharmaceutical Industries

Shelf life: 24 months

Storage conditions: Do not store above 30°C

Registration No.: 1207210858 - 1207210859

Decision and Decision Date: Approved on 26/03/2021

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1. Terms, Definitions, Abbreviations

Terms	Definitions
AUC_{0-t}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time 0 to infinite time
C.I	Confidence Intervals
C_{max}	Maximum serum concentration
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
INN	International Nonproprietary Names
SFDA	Saudi Food and Drug Authority
SA	Saudi Arabia
SDI	Saudi Drug Information System
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
USAN	United States Adopted Names

Leukair ®

2. Background

2.1 Submission Details

Type of submission: Human Generic Drug

Reference product in SA: Singulair

Pharmacological class: Leukotriene receptor antagonist

Submitted Indication:

Leukair 4 mg is indicated for the following indications:

- 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.
- 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.
- Indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

Leukair 5 mg is indicated for the following indications:

- 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.
- 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.

- Indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Submitted Dosage: 4 mg -5 mg

2.2 Regulatory Background

This product is considered a human generic drug for Saudi regulatory purposes.

Furthermore, this product is qualified to follow the regular review pathway normal submission.

2.3 Product Information

The officially approved Summary of Product Characteristics (SPC) can be accessed via Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3. Scientific discussion about the product:

3.1 Quality Aspects

3.1.1 Drug Substance

- Montelukast Sodium is a white to pale yellow powder. Montelukast Sodium is freely soluble in methanol, soluble in water and practically insoluble in acetonitrile at 25°C±2°C. Montelukast Sodium has/possesses one chiral center. Polymorphism has been observed.
- The drug substance is manufactured by multiple-step chemical synthesis.
- The structure of Montelukast Sodium has been fully elucidated using several spectroscopic techniques.
- The drug substance specification includes relevant tests for proper quality control. The control methods are validated according to international guidelines.
- Appropriate stability data have been presented and justified the established re-test period.

3.1.2 Drug Product

- Montelukast Sodium chewable tablets is available in two strengths:

  1. 4 mg tablet: Pink colour, oval, biconvex, uncoated chewable mottled tablet debossed with 'CL 55' on one side and plain on the other side.
  2. 5 mg tablet: Pink colour, mottled, circular, biconvex, uncoated chewable tablet debossed with 'CL 56' on one side and plain on the other side.

- Each tablet contains 4 mg or 5 mg of Montelukast (4.16 mg or 5.187 mg ≈ 5.2 of Montelukast Sodium). The composition of the drug product is adequately described, qualitatively and quantitatively. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

- The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

- The drug product specification covers appropriate parameters for this dosage form which allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show a consistent quality of the drug product.

- The drug product is packaged in a carton box, containing 3 cold formAlu - Alu blisters, with 10 tablets in each blister.

- Appropriate stability data have been generated in the packaging material intended for commercial use and following relevant international guidelines. The data show good stability of the finished product and support the shelf life.

3.2 Clinical Aspects

3.2.1 Bioequivalence study

A randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Leukair® (Montelukast sodium) 5 mg of Macleods

Pharmaceuticals Ltd., India and Singulair® (Montelukast sodium) 5 mg of Merck & Co. Inc., USA in healthy human adult subjects, under fasting condition. The study was conducted in accordance with GCC Guidelines for Bioequivalence, standards of Good Clinical Practice (GCP) and Good Laboratory Practices (GLP).

Blood samples were taken pre-dose (0.0) and at a specified time points up to 32 hours after administration of test or reference product. Plasma levels of Montelukast were detected by a validated LC-MS/MS method.

Twenty nine (29) volunteers completed the study and all data were analyzed. No significant protocol deviations were reported. There were no serious adverse events reported in the study.

The ratio and 90% Confidence Intervals of Test versus Reference for Montelukast are tabulated below:

Table 1: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Montelukast sodium:

Pharmacokinetic Parameter	**Point Estimate**	**90% Confidence Intervals (%)**
C_{max}	98.66	91.67 - 106.19
AUC_{0-t}	99.22	94.11 - 104.62
$AUC_{0-\infty}$	99.21	94.14 - 104.55

Based on the results obtained in this study, Leukair® (Montelukast sodium) 5 mg of Macleods Pharmaceuticals Ltd., India, is **bioequivalent** to Singulair ® (Montelukast sodium) 5 mg of Merck & Co. Inc., USA, under fasting conditions.

4. Risk Management Plan

4.1 Artwork and Trade Name assessment (Artwork available in appendix)

Proposed trade Name	Dosage Form
LEUKAIR	Gastro-resistant Tablets

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

LEUKAIR name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN International Nonproprietary Names and USAN United States Adopted Names STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
LEUKAIR	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name LEUKAIR is accepted.

Outer and Inner Package:

Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on data reviewed from a quality, safety and efficacy perspective, the SFDA considered that the benefit/risk profile of LEUKAIR was favorable and decided to grant the marketing authorization of LEUKAIR for the treatment of:

Leukair 4 mg:

- 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.
- 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.
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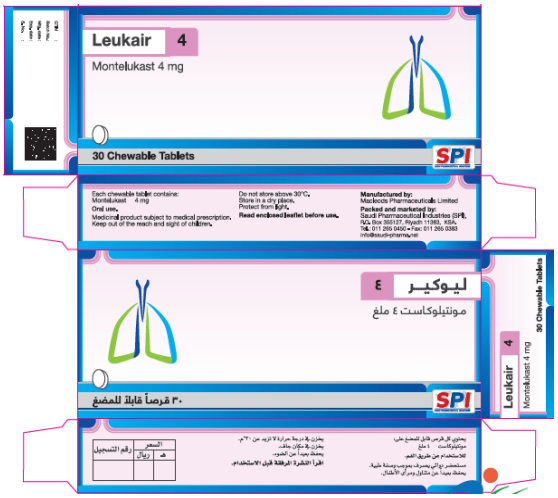
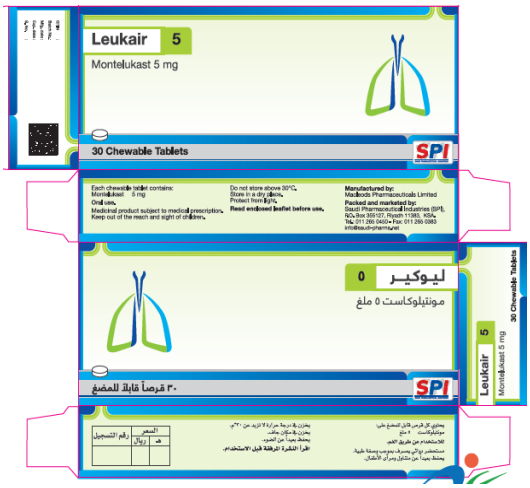
Leukair 5 mg

- 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.
- 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.
- Indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

6. Appendix





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The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published only at SDI.

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa