Saudi Public Assessment Report

Gizamlo®

Active Pharmaceutical Ingredient(s): Irbesartan, Amlodipine Besilate

ATC code/CAS no.: C09 DB 05

Pharmaceutical/Dosage Form: Film-Coated Tablet

Dosage Strength: 300, 10 mg – 300, 5 mg - 150, 5 mg

Marketing Authorization Holder: Dar Aldawa

Shelf life: 24 months

Storage conditions: Store below 30°C.

Registration No.: 0604221921 - 0604221922 - 0604221923

Decision and Decision Date: Approved on 14/02/2022

Table of Contents

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
DAD	Dar Al Dawa
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
INN	International Nonproprietary Names
SA	Saudi Arabia
SDI	Saudi Drug Information System
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
USAN	United States Adopted Names

2. Background

2.1 Submission Details

Type of submission: Human Generic Drug

Reference product in SA:

- Aprovasc 300mg/5mg Film coated tablets
- Aprovasc 300mg/10 mg Film coated tablets
- Aprovasc 150 mg/5 mg Film coated tablets

Pharmacological class: Angiotensin-II antagonists, plain

Submitted Indication: Treatment of essential hypertension. Gizamlo is indicated in patients whose blood pressure is not adequately controlled on irbesartan or amlodipine monotherapy.

Submitted Dosage:

- Gizamlo 150 mg /5 mg Film coated tablets
- Gizamlo 300 mg /5 mg Film coated tablets
- Gizamlo 300 mg /10 mg Film coated tablets

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.

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

Amlodipine Besilate:

- Amlodipine Besilate is a white or almost white powder. Amlodipine Besilate is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and

slightly soluble in 2-propanol. Amlodipine Besilate does have one chiral center. Polymorphism has been observed.

- The drug substance is manufactured by a multiple-step chemical synthesis.
- The structure of Amlodipine Besilate 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 justify the established re-test period.

Irbesartan:

- Irbesartan is a white or almost white crystalline powder. Irbesartan is practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol and in methylene chloride. Irbesartan does not have any chiral center. Polymorphism has been observed.
- The drug substance is manufactured by a multiple-step chemical synthesis.
- The structure of Irbesartan 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 justify the established re-test period.

3.1.2 Drug Product

- Gizamlo drug product is available in three strengths:

1. 300/5 mg Fim Coated Tablet: Yellow oval – shaped film coated tablets coded DAD on one side and plain on the other side.

2. 300/10 mg Fim Coated Tablet: White oval – shaped film coated tablets coded DAD on one side and plain on the other side.
3. 150/5 mg Fim Coated Tablet: White oval – shaped film coated tablets coded DAD on one side and plain on the other side.

- 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 consistent quality of the drug product.
- The drug product is packaged in carton box, containing 3 Alu/Alu blisters, each blister contains 10 tablets
- 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 Gizamlo® (Irbesartan / Amlodipine) 300 mg/10 mg of Dar Al Dawa (DAD), Jordan and Aprovasc® (Irbesartan / Amlodipine) 300 mg/10 mg of Sanofi-Aventis de Mexico SA.de C.V , Mexico, in healthy human adult subjects, under fasting condition. The study was conducted in accordance with Gulf Cooperation Council (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 72 hours after administration of test or reference product. Plasma levels of Irbesartan and Amlodipine were detected by a validated LC-MS/MS method.

Thirty-four (34) 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 Irbesartan and Amlodipine are tabulated below:

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

Pharmacokinetic Parameter	Point Estimate	90% Confidence Intervals (%)
C_{max}	102.48	93.07 – 112.83
AUC_{0-t}	101.24	92.1 – 111.29
$AUC_{0-\infty}$	101.29	91.99 – 111.53

Table 2: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Amlodipine:

Pharmacokinetic Parameter	Point Estimate	90% Confidence Intervals (%)
C_{max}	101.28	97.18 – 105.55
AUC_{0-72}	100.43	96.52 – 104.49

Based on the results obtained in this study, Gizamlo® (Irbesartan / Amlodipine) 300 mg/10 mg of Dar Al Dawa (DAD), Jordan, is **bioequivalent** to Aprovasc® (Irbesartan / Amlodipine) 300 mg/10 mg of Sanofi-Aventis de Mexico S.A.de C.V, Mexico, under fasting conditions.

4. Risk Management Plan

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

Proposed trade Name	Dosage Form
Gizamlo	Tablets

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

Gizamlo 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
Gizamlo	NO	NO	NO	NO

Trade Name Recommendation:

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

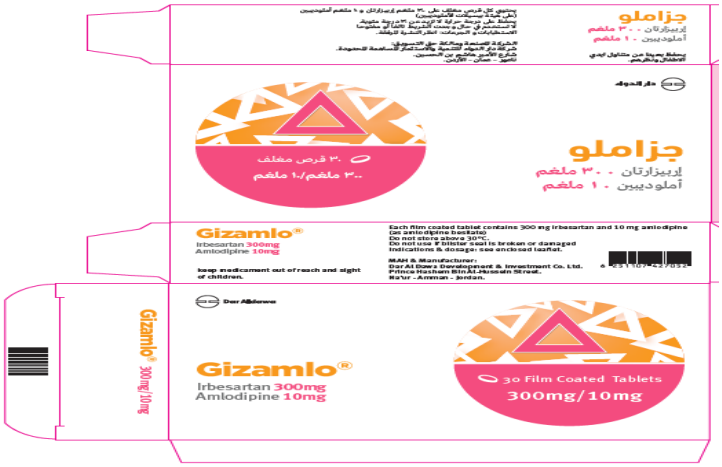
Outer and Inner Package:

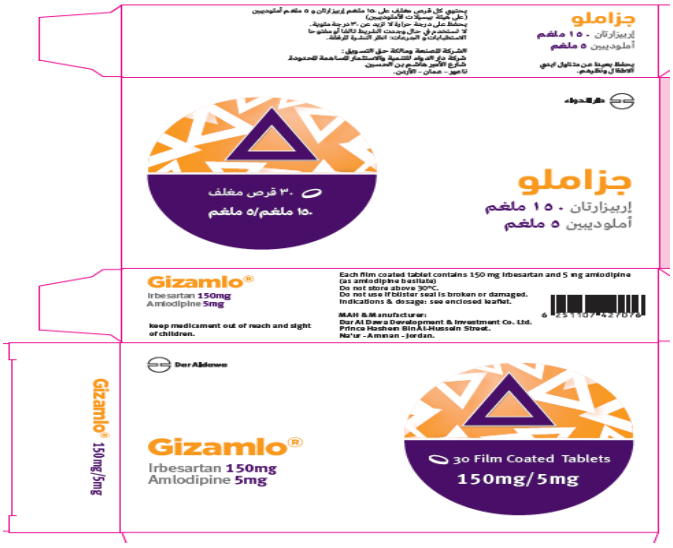
Based on the submitted data, the proposed artwork is accepted.

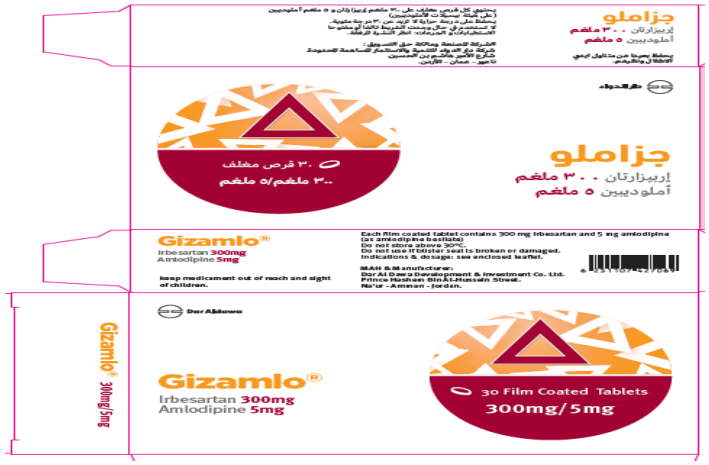
5. Overall Conclusion

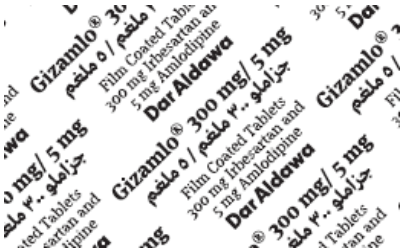
Based on a review of data on quality, safety and efficacy, SFDA considered that the benefit/risk profile of Gizamlo was favorable and decided to grant the marketing authorization of Gizamlo for the treatment of essential hypertension. Gizamlo is indicated in patients whose blood pressure is not adequately controlled on irbesartan or amlodipine monotherapy.

6. Appendix









Gizamlo®

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 at (SDI or Summary Saudi-PAR report).

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