Saudi Public Assessment Report

Gizlan HCT®

Active Pharmaceutical Ingredient(s): Irbesartan - Hydrochlorothiazide

ATC code/CAS no.: C09DA04

Pharmaceutical/Dosage Form: Film Coated Tablets

Dosage Strength: 300/12.5 mg - 300/25 mg - 150 /12.5 mg

Marketing Authorization Holder: Dar Al Dawa Development & Investment Co. Ltd.

Shelf life: 24 Months

Storage conditions: Do not store above 30° C.

Registration No.: 2812211517, 2812211515, 0410211104

Decision and Decision Date: Approved on 19/04/2021

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
CI	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: CoAprovel Film-coated tablet.

Pharmacological class: Angiotensin-II Antagonists, Diuretic, Combinations

Submitted Indication: Treatment of essential hypertension. This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

Submitted Dosage: 300/12.5 mg - 300/25 mg - 150 /12.5 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 normal submission regulatory 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

Irbesartan:

- Irbesartan is a white to almost white crystalline powder. Irbesartan is sparingly soluble in methanol; practically insoluble in water, slightly soluble in ethanol 96% and methylene chloride. Irbesartan does not have any chiral centers. 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.

Hydrochlorothiazide:

- Hydrochlorothiazide is a white or almost white crystalline odorless powder. Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide does not have any chiral centers Polymorphism has been observed.

- The drug substance is manufactured by a multiple-step chemical synthesis.

- The structure of hydrochlorothiazide 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

- Gizlan HCT® drug product is available in three strengths:

1. 150mg/12.5mg film coated tablet: Pink oval – shaped film coated tablet coded C109 on one side, plain on the other side. Each tablet contains 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

2. 300mg/12.5mg film coated tablet: Pink oval – shaped film coated tablet coded C117 on one side, plain on the other side. Each tablet contains 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

3. 300mg/25mg film coated tablet: Pinkish brown oval – shaped film coated tablet coded C108 on one side, plain on the other side. Each tablet contains 300 mg of irbesartan and 25 mg of hydrochlorothiazide.

- 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 Alu/Alu blisters, containing 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 Gizlan HCT® (Irbesartan/ Hydrochlorothiazide) 300 mg /25 mg of Dar Al Dawa (DAD), Jordan and Coaprovel® (Irbesartan/ Hydrochlorothiazide) 300 mg /25 mg of Sanofi Winthrop Industrie, France, 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 Hydrochlorothiazide were detected by a validated LC-MS/MS method.

Thirty-nine (39) 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 (CI) of Test versus Reference for Irbesartan and Hydrochlorothiazide are tabulated below:

Table 1: Ratio and 90% (CI) of Test versus Reference for Irbesartan:

Pharmacokinetic Parameter	Point Estimate	90% Confidence Intervals (%)
C_{max}	103.524	96.665 - 110.870
AUC_{0-t}	113.034	105.123 - 121.541
$AUC_{0-\infty}$	112.691	104.728 - 121.259

Table 2: Ratio and 90% (CI) of Test versus Reference for Hydrochlorothiazide:

Pharmacokinetic Parameter	Point Estimate	90% Confidence Intervals (%)
C_{max}	108.401	97.868 - 120.068
AUC_{0-t}	102.499	96.456 - 108.920
$AUC_{0-\infty}$	102.482	96.097 - 109.292

Based on the results obtained in this study, Gizlan HCT® (Irbesartan/ Hydrochlorothiazide) 300 mg /25 mg of Dar Al Dawa (DAD), Jordan, is **bioequivalent** to Coaprovel® (Irbesartan/ Hydrochlorothiazide) 300 mg /25 mg of Sanofi Winthrop Industrie, France, under fasting conditions.

4. Risk Management Plan

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

Proposed trade Name	Dosage Form
Gizlan HCT®	FCT

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

Gizlan HCT® 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
Gizlan HCT®	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Gizlan HCT® is accepted.

Outer and Inner Package:

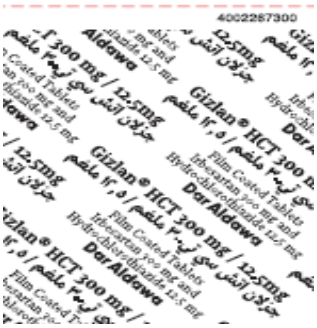
Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on the reviewed data from quality, safety and efficacy. The SFDA considered that the benefit/risk profile of Gizlan HCT® was favorable and decided to grant the marketing authorization of Gizlan HCT® for the treatment of essential hypertension. This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

6. Appendix


جزلان اتش سي تي
إربيزارتان ٣٠٠ ملغم
هيدروكلوروثيازايد ١٢,٥ ملغم
٣٠ قرص مغلف
٣٠٠ ملغم/ ١٢,٥ ملغم
Gizlan® HCT
Irbesartan 300 mg
Hydrochlorothiazide 12.5 mg
Dar Aldawa
30 Film Coated Tablets
300 mg/12.5mg
Gizlan® HCT 300 mg/12.5mg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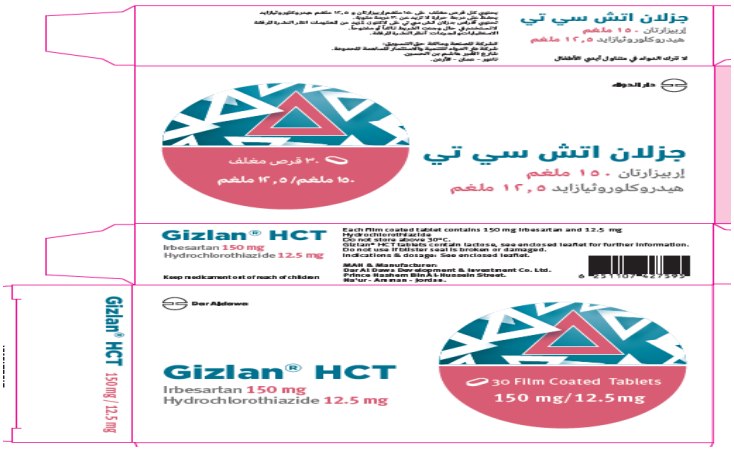
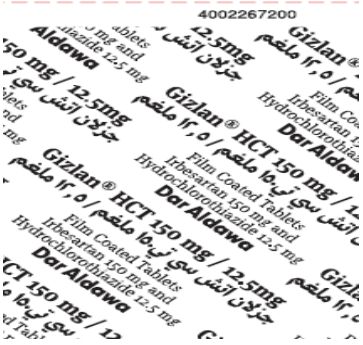
Aldawa
Gizlan® HCT 300 mg / 12.5mg
Dar Aldawa


جزلان اتش سي تي
إربيزارتان ١٥٠ ملغم
هيدروكلوروثيازايد ١٢,٥ ملغم
٣٠ قرص مغلف
١٥٠ ملغم/ ١٢,٥ ملغم
Gizlan® HCT
Irbesartan 150 mg
Hydrochlorothiazide 12.5 mg
Dar Aldawa
30 Film Coated Tablets
150 mg/12.5mg
Gizlan® HCT 150mg/12.5mg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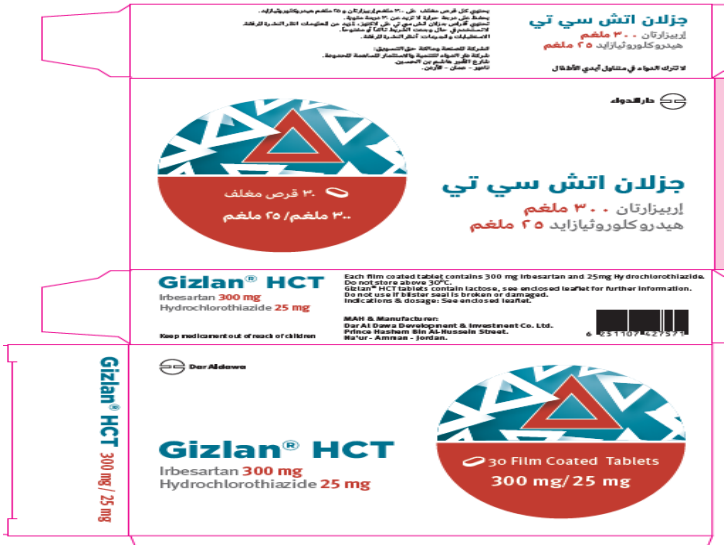
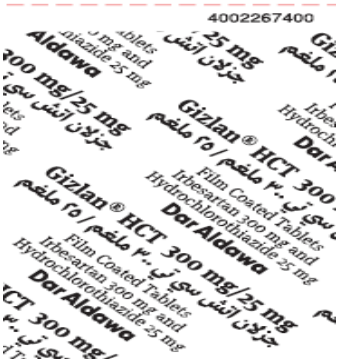
Aldawa
Gizlan® HCT 150 mg / 12.5mg
Dar Aldawa


جزلان اتش سي تي
إربيزارتان ٣٠٠ ملغم
هيدروكلوروثيازايد ٢٥ ملغم
٣٠ قرص مغلف
٣٠٠ ملغم/ ٢٥ ملغم
Gizlan® HCT
Irbesartan 300 mg
Hydrochlorothiazide 25 mg
Dar Aldawa
30 Film Coated Tablets
300 mg/25 mg
Gizlan® HCT 300 mg/25 mg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Aldawa
Gizlan® HCT 300 mg/25 mg
Dar Aldawa

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