الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Acloran Plus®

Type of Application: New Drug Application.

Type of Product: Human New Drug.

Active Pharmaceutical Ingredient(s): Candesartan Cilexetil, Amlodipine Besilate, Hydrochlorothiazide

ATC code: C09DX06.

Dosage Form: Capsule.

Dosage Strength:
16 mg ,5 mg ,12.5 mg
16 mg,10 mg,12.5 mg

Pack Size: 30

Shelf life: 24 months

Storage Conditions: Do not store above 30°C

Reference Product in SA (if applicable): Atacand, Norvasc, Esidrex

Marketing Authorization Holder: MS Pharma Saudi (MSPS)

Manufacturer: ADAMED Pharma S.A

Registration No.: 2812234637, 2812234638

Date of Decision: 28/12/2023

Proposed Indications:

Acloran Plus® is indicated for the:

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of Candesartan, Amlodipine, and Hydrochlorothiazide, taken either as three single-component formulations or as a dual-component and a single-component formulation.

Acloran Plus® should not be used as initial therapy.

Product Background

This product is considered as a known active ingredient drug for Saudi regulatory purposes qualified to follow the SFDA's regulatory Regular pathway .

The SFDA approval for Acloran Plus® is based on a review of the quality, safety and efficacy of the product provided as an e-CTD in accordance with the relevant guidelines, basic product information summarized hereinafter:

Quality Aspects

Drug Substance

Candesartan cilexetil

- Candesartan cilexetil is a white or almost white crystalline powder. Candesartan cilexetil is freely soluble in chloroform and tetrahydrofuran, soluble in acetone, slightly soluble in methanol and acetonitrile, practically insoluble in water. Its solubility in aqueous solution is pH dependent. Polymorphism has been observed (Form I).
- The drug substance is manufactured by a multiple-step chemical synthesis.
- The structure of Candesartan cilexetil 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.

Amlodipine besilate

- Amlodipine besilate is a white or almost white powder Amlodipine besilate is Freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in water and in 2-propanol . Polymorphism has been observed (Crystalline Nonhydrate form.).
- 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.

Hydrochlorothiazide

- Hydrochlorothiazide is a white or almost white, crystalline powder. Hydrochlorothiazide is Very slightly soluble in water, soluble in acetone, sparingly soluble in 96% ethanol. Dissolves in dilute solutions of alkali hydroxides. Polymorphism has been observed (Form I).

- 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.

Drug Product

- The drug product is available in two strengths:
    1. 16mg/10mg/12.5mg Capsules: Hard gelatin capsule of size “0”; white body imprinted with black “1”, orange cap imprinted with black “CAH”, filled with white to off-white powder.
    2. 16mg/5mg/12.5mg Capsules: Hard gelatin capsule of size “0”; white body imprinted with black “2”, red cap imprinted with black “CAH”, filled with white to off-white powder.
- Each capsule contains 16 mg of candesartan cilexetil, 10 mg unit of amlodipine as amlodipine besylate, and 12.5 mg of hydrochlorothiazide <OR> 16 mg of candesartan cilexetil, 5 mg unit of amlodipine as amlodipine besylate, and 12.5 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 consistent quality of the drug product.
- The drug product is packaged in blisters, consisting of Polyamide-Aluminium- PVC (laminate) and aluminium lidding foil in a carton box with folded leaflet. In pack size of 30 hard capsules per pack (10 hard capsules per 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.
-

Clinical Aspects

Bioequivalence Study

Ratio and 90% Confidence Intervals (CI) of Acloran Plus® (Candesartan cilexetil /Amlodipine /Hydrochlorothiazide) 16/10/12.5 mg Hard Capsule versus Atacad® (Candesartan) 16 mg, Norvasc® (Amlodipine) 10 mg and Esidrex® (Hydrochlorothiazide) 12.5 mg Tablet:

For Candesartan

Pharmacokinetic Parameter	Point Estimate	90% CI
C_{max}	88.97	82.53 - 95.91
AUC_{0-t}	99.70	95.72 - 103.86

For Amlodipine

Pharmacokinetic Parameter	Point Estimate	90% CI
C_{max}	101.92	97.26-106.80
AUC_{0-t}	104.07	99.90-108.42

For Hydrochlorothiazide

Pharmacokinetic Parameter	Point Estimate	90% CI
C_{max}	114.57	108.26-121.25
AUC_{0-t}	100.68	97.73-103.72

Based on the results obtained in this study, Acloran Plus® (Candesartan cilexetil /Amlodipine /Hydrochlorothiazide) 16/10/12.5 mg Hard Capsule of Adamed Pharma S.A., Poland is **bioequivalent** to Atacad® (Candesartan) 16 mg of Takeda Pharmaceutical Company Ltd., Japan, Norvasc® (Amlodipine) 10 mg of Pfizer Manufacturing Deutschland GmbH, Germany and Esidrex® (Hydrochlorothiazide) 12.5 mg Tablet of Cenexi, France under Fasting Conditions.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

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