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Autoridade Nacional do Medicamento
e Produtos de Saúde I.P.

Summary Public Assessment Report

Generics

Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets

(Candesartan cilexetil + Hydrochlorothiazide)

PT/H/1217/001-002/DC

Date: 25-08-2016

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This is a summary of the public assessment report (PAR) for Candesartan+Hidroclorotiazida Tchaikapharma. It explains how Candesartan+Hidroclorotiazida Tchaikapharma 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 Candesartan+Hidroclorotiazida Tchaikapharma.

For practical information about using Candesartan+Hidroclorotiazida Tchaikapharma patients should read the package leaflet or contact their doctor or pharmacist.

What is Candesartan+Hidroclorotiazida Tchaikapharma and what is it used for?

Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets is a 'generic medicine'. This means that Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets is similar to a 'reference medicine' already authorised in the European Union (EU) called Hytacand 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets (In RMS: Portugal).

It is used for treating high blood pressure (hypertension) in adult patients.

Your doctor may prescribe Candesartan+Hidroclorotiazida Tchaikapharma if your blood pressure has not been properly controlled by candesartan or hydrochlorothiazide alone.

Candesartan+Hidroclorotiazida Tchaikapharma can be used to treat adult heart failure patients with reduced heart muscle function when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used or in addition to ACE-inhibitors when symptoms persist despite treatment and mineralocorticoid receptors antagonists (MRA) cannot be used.

(ACE-inhibitors and MRAs are medicines used to treat heart failure).

You must talk to a doctor immediately if you do not feel better or if you feel worse.

How does Candesartan+Hidroclorotiazida Tchaikapharma work?

The name of your medicine is Candesartan+Hidroclorotiazida Tchaikapharma. It is used for treating high blood pressure (hypertension) in adult patients. It contains two active ingredients: candesartan and hydrochlorothiazide. These work together to lower your blood pressure.

- Candesartan belongs to a group of medicines called angiotensin II receptor antagonists. It makes your blood vessels relax and widen. This helps to lower your blood pressure.
- Hydrochlorothiazide belongs to a group of medicines called diuretics (water tablets). It helps your body to get rid of water and salts like sodium in your urine. This helps to lower your blood pressure.

How is Candesartan+Hidroclorotiazida Tchaikapharma used?

The pharmaceutical form of Candesartan+Hidroclorotiazida Tchaikapharma is tablets and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Candesartan+Hidroclorotiazida Tchaikapharma have been shown in studies?

Because Candesartan+Hidroclorotiazida Tchaikapharma is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Hytacand Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
The company provided data from the published literature on Candesartan cilexetil + Hydrochlorothiazide.

What are the possible side effects of Candesartan+Hidroclorotiazida Tchaikapharma?

Because Candesartan+Hidroclorotiazida Tchaikapharma is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

Why is Candesartan+Hidroclorotiazida Tchaikapharma approved?

It was concluded that, in accordance with EU requirements, Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets has been shown to have comparable quality and to be bioequivalent/be comparable to Hytacand 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets. Therefore, the INFARMED, I.P. decided that, as for <reference medicine called Hytacand 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Candesartan+Hidroclorotiazida Tchaikapharma?

A Risk Management Plan - Version and Date: Version 01 - September 2013 has been developed to ensure that Candesartan+Hidroclorotiazida Tchaikapharma is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package

leaflet for Candesartan+Hidroclorotiazida Tchaikapharma, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Candesartan+Hidroclorotiazida Tchaikapharma

The marketing authorisation for Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets was granted on **25-08-2016.**

The full PAR for Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets can be found on the website http://www.infarmed.pt/infomed/inicio.php. For more information about treatment with Candesartan+Hidroclorotiazida Tchaikapharma, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in MM-YYYY.

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Public Assessment Report

Scientific discussion

Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets

(Candesartan cilexetil + Hydrochlorothiazide)

PT/H/1217/001-002/DC

Date: 25-08-2016

This module reflects the scientific discussion for the approval of Candesartan+Hidroclorotiazida Tchaikapharma. The procedure was finalised at 22-04-2015. For information on changes after this date please refer to the module 'Update'.

I. Introduction

Based on the review of the quality, safety and efficacy data, the Member States have agreed in granting a marketing authorisation for Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets, from Tchaikapharma High Quality Medicines Inc.

Candesartan+Hidroclorotiazida Tchaikapharma is indicated for the:

Treatment of essential hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy

Posology

The recommended dose of Candesartan/ Hydrochlorothiazide is one tablet once daily.

Dose titration with the individual components (candesartan cilexetil and hydrochlorothiazide) is recommended. When clinically appropriate a direct change from monotherapy Candesartan+Hidroclorotiazida Tchaikapharma may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy. Candesartan+Hidroclorotiazida Tchaikapharma may be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy or Candesartan+Hidroclorotiazida Tchaikapharma at lower doses
Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised application concerns a generic version of fixed combination of candesartan cilexetil and hydrochlorothiazide in two dose strengths: 8 mg + 12,5 mg and 16 mg + 12,5 mg.
This marketing authorisation application for Candesartan + Hidroclorotiazida Tchaikapharma (candesartan cilexetil + hydrochlorothiazide; 8 mg + 12,5 mg and 16 mg + 12,5 mg; tablets) is submitted under Article 28(3) Directive 2001/83/EC Article 10 (1) generic application.

The originator product is Atacand Plus (and associated names), 8 mg + 12,5 mg and 16 mg + 12,5 mg, tablets marketed by AstraZeneca, registered since November 1998 (first Marketing Authorization granted throughout Europe).
In Portugal, the reference medicinal product is Hytacand 8 mg + 12,5 mg and 16 mg + 12,5 mg tablets, marketed by AstraZeneca Produtos Farmacêuticos, Lda, authorised in 30-04-2009.

The marketing authorization was granted on **25-08-2016** based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Tchaikapharma High Quality Medicines Inc.

With Portugal as the Reference Member State in this decentralized procedure, Tchaikapharma High Quality Medicines Inc, is applying for the Marketing Authorizations for Candesartan + Hidroclorotiazida Tchaikapharma 8 mg + 12,5 mg and 16 mg + 12,5 mg tablets, in BG, CZ, EL, PL, RO, SK.

The generic product has the same composition in terms of the active substances and the same pharmaceutical form as the reference product.

II. Quality aspects

II.1 Introduction

The Pharmaceutical form is tablets

Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg tablets are white or off white, oval, biconvex (~9,5 x4,5 mm), uncoated tablets, with a score line on one side.

Candesartan+Hidroclorotiazida Tchaikapharma 16 mg + 12.5 mg tablets are peach, oval, biconvex (~9,5 x 4,5 mm), uncoated tablets, with a score line on one side.

The tablet can be divided into equal doses.

The other excipients are:

Mannitol, Maize Starch, Copovidone (K25-31), Glycerol, Magnesium Stearate

Candesartan+Hidroclorotiazida Tchaikapharma 16 mg + 12.5 mg tablets contains also Ferric oxide, yellow (E172) and Ferric oxide, red (E172).

Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg tablets is available in OPA/Alu/PVC-Aluminium blister packs of 30 tablets.

Candesartan+Hidroclorotiazida Tchaikapharma 16 mg + 12.5 mg tablets is available in OPA/Alu/ PVC-Aluminium blister packs of 30 tablets.

II.2 Drug Substance

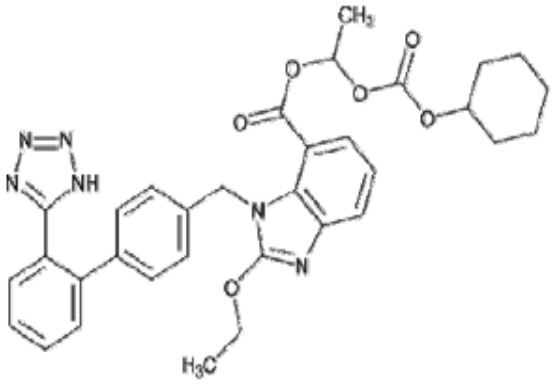
Candesartan cilexetil

General Information

Nomenclature
Candesartan cilexetil (INN) CAS Number: 145040-37-5.

Structure

The structural formula of Candesartan cilexetil is the following:



Molecular formula: $C_{33}H_{34}N_6O_6$
Molecular weight: 610.66

General Properties

Candesartan cilexetil is a white or almost white crystalline powder.
At 25°C, Candesartan cilexetil is freely soluble in chloroform and tetrahydrofuran, soluble in acetone, sparingly soluble in ethanol, slightly soluble in methanol and acetonitrile, practically insoluble in water. Its solubility in aqueous solution is pH dependent.Candesartan cilexetil is practically insoluble in the solution of the pH from 2.0 to 11.0, it become very slightly soluble when the pH increased to 12.0.
The DSC curve shows a minor endotherm of conversion at peak temperature of 169±5ºC.
The optical rotation of Candesartan cilexetil is between -0.10° and +0.10° (10 mg per ml, in methanol).
Candesartan cilexetil is not hygroscopic.
Two polymorphs, Form I (or Form C) and Form II, and one amorphous form were reported in literature. DSC, IR and X-ray Diffraction studies indicate that Zhejiang Huahai manufactured Candesartan Cilexetil yields Form I.
In the structure of Candesartan cilexetil, there is one asynisomer carbon existed, so theoretically, there is two isomers available, one is S-Candesartan cilexetil, another is R-Candesartan cilexetil. For huahai's product, it is racemate; the optical rotation is controlled at –0.10° and +0.10°.
Tested as per Ph. Eur. 2.6.12 and 2.6.13, Huahai's Candesartan Cilexetil could meet the requirement of Ph. Eur 5.1.4
Tested by verified light diffraction method (Ph.Eur. 2.9.31), representative diffraction pattern show Huahai's Candesartan Cilexetil with D90 about 30 μm, D50 about 15 μm, D10 about 5 μm.

Hydrochlorothiazide

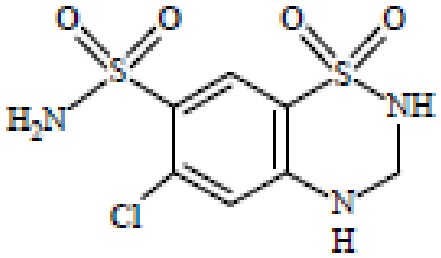
General Information

Nomenclature

Hydrochlorothiazide (INN)
Chemical name as per Ph Eur: 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide;

Structure

The structural formula of Hydrochlorothiazide is the following:



General Properties

Description:	White or almost white crystalline powder.
Isomerism :	Hydrochlorothiazide does not have any chiral center; hence does not exhibit optical isomerism.

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Candesartan + Hidroclorotiazida Tchaikapharma are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 24 months when Candesartan cilexetil drug substance is stored in the proposed container closure system is justified. The proposed retest period of 36 months when Hydrochlorothiazide drug substance is stored in the proposed container closure system is justified.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 12 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 30 months with without any special storage condition for the drug product is considered acceptable.

III. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of candesartan cilexetil and hydrochlorothiazide are well known. As candesartan cilexetil/hydrochlorothiazide is a widely used, well-known active substance combination, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The applicant has provided a revised version of the non-clinical overview, include information on non-clinical studies performed with the candesartan cilexetil/hydrochlorothiazide combination.
Concerning the SmPC, the contents of points 4.6 and 5.3 are identical to those encountered in the SmPC for the reference medicinal product.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. Clinical aspects

To support the application, the applicant has submitted as report two of bioequivalence studies.

- Study CDHT-BESD-07-TFB/10 - single dose study with 8/12,5mg tablets under fasting conditions

- Study CDHT-BESD-06-TFB/10 - single dose study with 32/25mg tablets under fasting conditions

The results of study CDHT-BESD-06-TFB/10 with the 32/25 mg formulation and study CDHT-BESD-07-TFB/10 with the 8/12.5 mg formulation can be extrapolated to other strengths 16/12.5 and 32/12.5, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets is considered bioequivalent with Hytacand 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets

IV.1 Risk Management Plan

The MAH has submitted a Risk Management Plan - Version and Date: Version 02 - March 2014, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets.

Important identified risks:
1. Renal artery stenosis
2. Hypotension
3. Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
4. Primary hyperaldosteronism
5. Electrolyte disorders- hypokalaemia, hypercalcaemia
6. Photosensitivity
7. Hyperuricaemia
8. Drug interaction- increased potassium loss in combination with kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates, steroids.

Important potential risks:
1. Use in patients with hepatic impairment
2. Use in patients with renal impairment
3. Foetotoxicity during pregnancy

IV.2 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

V. User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Atacand Plus 8/12.5 mg and 16/12.5 mg tablets which have been authorised via MRP, with day 90 on November 03, 1998 and Atacand Plus 32/12.5 mg and, 32/25 mg tablets as line extension on February 06, 2009 (SE/H/0162/001-004). The bridging report submitted by the applicant has been found acceptable.

VI. Overall conclusion, benefit/risk assessment and recommendation

The application for Candesartan+Hidroclorotiazida Tchaikapharma 8 mg + 12.5 mg and 16 mg + 12.5 mg tablets contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.