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Autoridade Nacional do Medicamento
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Summary Public Assessment Report

Entecavir Aurobindo

0.5 mg, 1 mg Film-coated tablets

(entecavir hydrate)

PT/H/1706/001-002/DC

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Entecavir 0.5 mg, 1 mg Film-coated tablets

This is a summary of the public assessment report (PAR) for Entecavir Aurobindo. It explains how Entecavir Aurobindo 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 Entecavir Aurobindo.

For practical information about using Entecavir Aurobindo, patients should read the package leaflet or contact their doctor or pharmacist.

What is Entecavir Aurobindo and what is it used for?

This decentralized procedure relates to Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets, according to Article 10.1 of Directive 2001/83/EC, claiming to be generic of the reference medicinal product Baraclude 0.5 mg & 1 mg, film-coated tablets, which is registered in the European Union by BRISTOL-MYERS SQUIBB PHARMA EEIG, as it has the same quantitative and qualitative composition in active substance and the same pharmaceutical form.

Entecavir Aurobindo tablets are anti-viral medicines, used to treat chronic (long term) hepatitis B virus (HBV) infection in adults.

How does Entecavir Aurobindo work?

Entecavir Aurobindo can be used in people whose liver is damaged but still functions properly (compensated liver disease) and in people whose liver is damaged and does not function properly (decompensated liver disease).
Entecavir Aurobindo tablets are also used to treat chronic (long term) HBV infection in children and adolescents aged 2 years to less than 18 years. Entecavir Aurobindo can be used in children whose liver is damaged but still functions properly (compensated liver disease).
Infection by the hepatitis B virus can lead to damage to the liver. Entecavir Aurobindo reduces the amount of virus in your body, and improves the condition of the liver.

How is Entecavir Aurobindo used?

The pharmaceutical form of Entecavir Aurobindo is film-coated 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 Entecavir Aurobindo have been shown in studies?

For generic medicines, studies in patients are limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Entecavir Aurobindo?

Because Entecavir Aurobindo 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.

For the full list of all side effects reported with Entecavir Aurobindo see section 4 of the package leaflet.

Why is Entecavir Aurobindo approved?
It was concluded that, in accordance with EU requirements, Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets has been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the INFARMED, I.P. decided that, as for reference medicine called Baraclude 0.5 mg & 1 mg, film-coated 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 Entecavir Aurobindo?
A Risk Management Plan (version 2.0) dated of January 2017 has been developed to ensure that Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets 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 Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets, 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 Entecavir Aurobindo
The marketing authorisation for Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets was granted on 28-06-2017.

The full PAR for Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets can be found on the website http://www.infarmed.pt/infomed/inicio.php. For more information about treatment with Entecavir Aurobindo 0.5 mg & 1 mg, film-coated tablets, read the package leaflet or contact your doctor or pharmacist.

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Public Assessment Report

Scientific discussion

Entecavir Aurobindo

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(entecavir hydrate)

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This module reflects the scientific discussion for the approval of Entecavir Aurobindo. The procedure was finalised at 21-06-2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Aurobindo Pharma (Portugal), Unipessoal Limitada has applied for a marketing authorization for paracetamol, in CZ, FR, DE, IT, NL, PL, RO, ES and UK.
Entecavir is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with:

- *Compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.*
- *Decompensated liver disease.*

Entecavir is also indicated for the treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.

The application is an abridged application according to Directive 2001/83/EC article 10.1 (a) (iii) first paragraph, claiming essential similarity. The Marketing Authorization was granted on 28-06-2017.

The originator product is Baraclude 0.5 mg & 1 mg, film-coated tablets, which is registered in the European Union by BRISTOL-MYERS SQUIBB PHARMA EEIG, since June 26th, 2006.

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.

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Aurobindo 0.5 mg film-coated tablets:
White triangular shaped (size 8.4 mm), biconvex, film-coated tablets, debossed with 'ET' on one side and '0 5' on the other side.

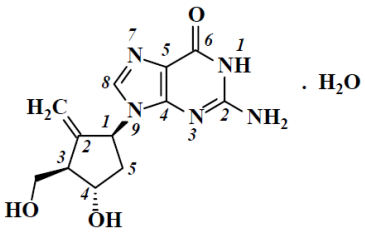
Entecavir Aurobindo 1mg film-coated tablets:
White round shaped (diameter 8.2 mm), biconvex, film-coated tablets, debossed with 'ET' on one side and '1' on the other side.

The excipients are
Tablet Core: Lactose monohydrate, Cellulose, microcrystalline (E460), Crospovidone (E1202), Magnesium stearate

Tablet coating: Hypromellose (E464), Macrogol 400, Titanium dioxide (E 171)

II.2 Drug Substance

Entecavir hydrate



Molecular formula: $C_{12}H_{15}N_5O_3 . H_2O$
Molecular weight: 295.29 (Entecavir monohydrate)

General Properties
Description: A white or almost white powder.
Solubility: Practically insoluble to slightly soluble in water, practically insoluble in anhydrous ethanol and in heptane, slightly soluble in methanol.
Polymorphism: Number of crystalline forms is reported in the literature. Aurobindo is manufacturing Entecavir monohydrate consistently.
Isomerism: Entecavir is having three chiral centres. Hence, total 2^3 = 8 stereoisomers are possible. Aurobindo is manufacturing (1S,3R,4S)–stereoisomer, which is similar to the innovator's marketed product.
Optical rotation: Between + 30.0° and + 38.0°
pKa: 14.64
Log P(Octanol/Water): (-) 1.73
pH: 7.9
Melting range: > 220ºC

II.3 Medicinal Product

The documentation provided complies with relevant EU guidelines and directives. Manufacture is performed in accordance with cGMP and consistency in quality and homogeneity is demonstrated.

The finished product specification is based on relevant development and stability studies. The development of the product has been described, the choice of excipients is justified and their functions explained.

Appropriate validation data have been provided for the analytical methods. Batch analyses data support the proposed finished product specification.

Stability studies were performed in line with the ICH guidance.

The shelf-life is 36 months when stored below 30ºC for the drug product packed in PVC/PVdC-Alu foil blister pack and without any special storage condition for the drug product packed in white opaque HDPE bottle pack with polypropylene closure.

Pack sizes:
Blister packs:30 and 90 film-coated tablets
HDPE packs: 30, 100 and 250 film-coated tablets.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Entecavir monohydrate are well known. As Entecavir monohydrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
An ERA was not submitted with this marketing authorization, based on the fact that this medicinal product does not result in an increase of the total quantity of both active substances into the environment. However, no information is available about the potential of this active substance to produce adverse environmental effects. This medicinal product should be used according to the precautions stated in the SmPC (6.6) in order to minimize any potential risks to the environment.

IV. CLINICAL ASPECTS

To support this application, the Applicant has submitted as report a single-dose bioequivalence study conducted in healthy subjects under fasting conditions with the strength of Entecavir 1 mg tablets (374-12) entitled:

"An open-label, randomized, two-treatment, single period, parallel, single dose comparative oral bioavailability study of Entecavir Tablets 1 mg (Test) of Aurobindo Pharma Limited, India and Baraclude Tablets 1 mg (Reference) of Bristol-Myers Squibb Pharma EEIG, UK in 84 healthy, adult, human subjects under fasting conditions."

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
A Risk Management Plan (version 2.0 – January 2017) for Entecavir Aurobindo, was submitted by the Applicant, according to GVP Module V for generic products.

User testing
The readability of the package leaflet was successfully demonstrated

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for *Entecavir Aurobindo* contains adequate quality, non-clinical and clinical data. A benefit/risk ratio comparable to the reference product can therefore be concluded.