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Public Assessment Report

Name of the Product:

Nadcad

0.5 mg, 1 mg film-coated tablets

(entecavir)

Procedure number: HU/H/0482/001-002/DC

Marketing authorisation holder: PharOs Pharmaceutical Oriented Services Ltd.

Date: 3 June 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the Member States have granted the marketing authorisation of the Nadcad 0.5 mg and 1 mg film-coated tablets. The holder of the marketing authorisation is PharOs Pharmaceutical Oriented Services Ltd.

The active substance is entecavir. Each film-coated tablet contains 0.5 mg or 1 mg entecavir (as monohydrate).

The other ingredients are:
- tablet core: lactose monohydrate, cellulose, microcrystalline (E460), hydroxypropyl-cellulose (E463), crospovidone Type A (E1202) and magnesium stearate (E470b);
- tablet coating: hypromellose (E464), macrogol 400 (E1521), titanium dioxide (E171) and (only in the 1 mg film-coated tablets) iron oxide red (E172).

Appearance:
- the 0.5 mg film-coated tablets are white to off-white, triangular-shaped, with "0.5" debossed on one side and plain on the other,
- the 1 mg film-coated tablets are pink, triangular-shaped, with "1" debossed on one side and plain on the other.

The products are supplied in cartons containing the film-coated tablets in unit-dose blisters or in bottles.

Nadcad film-coated tablets (further on: Nadcad) are anti-viral medicines, used to treat chronic (long term) hepatitis B virus (HBV) infection in adults. Nadcad 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).

Nadcad is also used to treat chronic (long term) HBV infection in children and adolescents aged 2 years to less than 18 years. Nadcad 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. Nadcad reduces the amount of virus in the body and improves the condition of the liver.

What patients need to know before taking Nadcad

Those who are allergic to entecavir or any of the other ingredients of this medicine should not take Nadcad.

Warnings and precautions

Patients should talk to their doctor before taking Nadcad:
- if they have ever had problems with the kidneys. This is important because Nadcad is eliminated from the body through the kidneys and such patients' dose or dosing schedule may need to be adjusted,
- if they would like to stop taking Nadcad. They must not do it without the doctor's advice since their hepatitis may worsen after stopping treatment. When the treatment with Nadcad is stopped, the doctor will continue to monitor the patient and take blood tests for several months,
- whether their liver functions properly and, if not, what the possible effects on the Nadcad treatment may be,
- if they are also infected with HIV (human immunodeficiency virus). Patients should not take Tacluv to treat their hepatitis B infection unless they are taking medicines for HIV at the same time, as the effectiveness of future HIV treatment may be reduced. Nadcad will not control the HIV infection,
- for taking Nadcad will not stop the patients from infecting other people with hepatitis B virus (HBV) through sexual contact or body fluids (including blood contamination). So, it is important to take appropriate precautions to prevent others from becoming infected with HBV. A vaccine is available to protect those at risk from becoming infected with HBV,
- for Nadcad belongs to a class of medicines that can cause lactic acidosis (excess of lactic acid in the blood) and enlargement of the liver. Symptoms such as nausea, vomiting and stomach pain might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. The doctor will monitor the patients regularly while they are receiving Nadcad,
- if they have previously received treatment for chronic hepatitis B.

Children and adolescents

Nadcad should not be used for children below 2 years of age or weighing less than 10 kg.

Other medicines and Nadcad

Patients should tell their doctor if they are taking, have recently taken or might take any other medicines.

Nadcad with food and drink

In most cases patients may take Nadcad with or without food. However, those who have had a previous treatment with a medicine containing the active substance lamivudine should consider the following. If the patient was switched over to Nadcad because the treatment with lamivudine was not successful, he/she should take Nadcad on an empty stomach once daily. If the patient's liver disease is very advanced, the doctor will also instruct him/her to take Nadcad on an empty stomach. Empty stomach means at least 2 hours after a meal and at least 2 hours before the next meal.

Children and adolescents (from 2 to less than 18 years of age) can take Nadcad with or without food.

Pregnancy, breast-feeding and fertility

Those who are pregnant or planning to become pregnant must consult their doctor. It has not been demonstrated that Nadcad is safe to use during pregnancy. Nadcad must not be used during pregnancy unless specifically directed by the doctor. It is important that women of childbearing age receiving treatment with Nadcad use an effective method of contraception to avoid becoming pregnant.

Patients should not breast-feed during treatment with Nadcad. They must inform their doctor if they are breast-feeding. It is not known whether entecavir, the active ingredient in this product, is excreted in human breast milk.

Driving and using machines

Dizziness, tiredness (fatigue) and sleepiness (somnolence) are common side effects which may impair the ability to drive and use machines. Those who have any concerns consult their doctor.

Nadcad contains lactose

This medicinal product contains lactose. Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

How to take Nadcad

Not all patients need to take the same dose of Nadcad. Patients should always take this medicine exactly as the doctor prescribed.

For adults, the recommended dose is either 0.5 mg or 1 mg once daily orally (by mouth).

This dose will depend on:
- whether the patient has been treated for HBV infection before, and what medicine he/she received,
- whether the patient has kidney problems. In this case the doctor may prescribe a lower dose for the patient or instruct him/her to take it less often than once a day,
- the condition of the liver.

For those who have been prescribed the 0.5 mg tablet, i.e. for children and adolescents (from 2 to less than 18 years of age): the child's doctor will decide the right dose based on the child's weight. Children weighing at least 32.6 kg may take the 0.5 mg tablet or an entecavir oral solution may be available. For patients weighing from 10 kg to 32.5 kg, an entecavir oral solution

is recommended. All dosing will be taken once daily orally (by mouth). There are no recommendations for Nadcad in children less than 2 years of age or weighing less than 10 kg. The child's doctor will decide the right dose based on the child's weight.

For those who have been prescribed the 1 mg tablet: for children and adolescents (from 2 to less than 18 years of age), Nadcad 0.5 mg tablets are available or an entecavir oral solution may be available. The child's doctor will decide the right dose based on the child's weight.

The doctor will advise the patient on the dose that is right for him/her. Patients should always take the dose recommended by their doctor to ensure that their medicine is fully effective and to reduce the development of resistance to treatment. Nadcad should be taken as long as your doctor has prescribed. The doctor will tell the patient if, and when he/she should stop the treatment.

Some patients must take Nadcad on an empty stomach (see section "Nadcad with food and drink")**.** If the doctor instructs the patient to take Nadcad on an empty stomach, empty stomach means at least 2 hours after a meal and at least 2 hours before the next meal.

What to do if you more Nadcad has been taken than it should have been?

The doctor must be contacted at once.

What to do if taking Nadcad has been forgotten?

It is important that patients do not miss any dose. Those who miss a dose of Nadcad, take it as soon as possible, and then take the next scheduled dose at its regular time. If it is almost time for the next dose, the missed dose should not be taken. The patient should wait and take the next dose at the regular time. No double dose must be taken to make up for a forgotten dose.

Patients must not stop Nadcad without their doctor's advice

Some people get very serious hepatitis symptoms when they stop taking Nadcad. Patients should tell their doctor immediately about any changes in symptoms that they notice after stopping treatment.

Possible side effects

Like all medicines, Nadcad can cause side effects, although not everybody experiences them.

Patients treated with Nadcad have reported the following side effects:
- common (at least 1 in 100 patients): headache, insomnia (inability to sleep), fatigue (extreme tiredness), dizziness, somnolence (sleepiness), vomiting, diarrhoea, nausea, dyspepsia (indigestion), and increased blood levels of liver enzymes,

- uncommon (at least 1 in 1,000 patients): rash, hair loss.
- rare (at least 1 in 10,000 patients): severe allergic reaction.

How to store Nadcad

This medicinal product does not require any special storage conditions, but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Nadcad 0.5 mg and 1 mg film-coated tablets. The procedure was finalised at 16 March 2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Cyprus) concerned the generic version of entecavir 0.5 mg and 1 mg film-coated tablets (Nadcad tablets).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator (and reference) products are Baraclude® 0.5 mg and 1 mg film coated tablets (Bristol-Myers Squibb Pharma EEIG). Baraclude® has been centrally authorised in the European Economic Area since 2006.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Nadcad 0.5 mg and 1 mg film-coated tablets from PharOs Pharmaceutical Oriented Services Ltd., Greece.

The products are 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.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

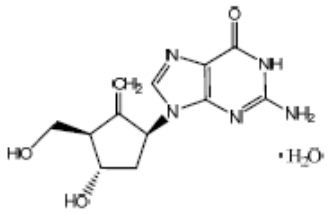
This chemical-pharmaceutical assessment report concerns the application of entecavir 0.5 mg and 1 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

The reference products are Baraclude film-coated tablets (containing 0.5 mg and 1 mg of entecavir as active ingredient) which were the original products of Bristol-Myers Squibb Pharma EEIG.

II.2 Drug substance

Data on the quality and manufacture of the drug substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorisation dossier. The Quality Overall Summary is adequate.

INN name: entecavir monohydrate
Chemical name: 2-Amino-9-[(1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6H-purin-6-one monohydrate
Structure:



The drug substance is a white or almost white crystalline powder, practically insoluble in acetonitrile and n-heptane, slightly soluble in methanol, ethanol and water, sparingly soluble in N,N-dimethylformamide, soluble in N,N-dimethylacetamide. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by IR, mass spectrometry, ultraviolet spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents, and catalysts.

The substance is specified by the drug product manufacturer according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph, additional specifications have been

set for lead content, residual solvents, polymorphism, particle size distribution and microbiological purity.

The Ph. Eur. specification includes the following tests for entecavir monohydrate: appearance, identification by IR and optical rotation, water content, sulphated ash, related substances by HPLC, assay by HPLC.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods, and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable if preserved in an airtight, light-resistant container.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing entecavir as drug substance in 0.5 mg and 1 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Baraclude 0.5 mg and 1 mg film-coated tablets, the branded original products of Bristol-Myers Squibb Pharma EEIG.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies, products with the following appearance were obtained:

- 0.5 mg: white to off-white and triangular-shaped film-coated tablet with “0.5” debossed on one side and plain on the other, with dimensions 8.4 mm x 8.7 mm ± 7.5 %,
- 1 mg: pink and triangular-shaped film coated tablet with “1” debossed on one side and plain on the other, with dimensions 10.6 mm x 11.0 mm ± 7.5 %.

The excipients used in the finished product are lactose monohydrate, microcrystalline cellulose, crospovidone Type A, hydroxypropylcellulose, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, and (only in the 1 mg formulation) red iron oxide. All excipients used comply with their respective Ph. Eur. monograph, except for Iron oxide red which complies with EU 231/2012. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the products are Aluminium-OPA/Alu/PVC blisters (triplex system) or HDPE bottles. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is approved, with 30 days storage period after the first opening of the HDPE bottles if stored below 25°C.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the products.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of entecavir are well known. As entecavir is a widely used, well-known active substance, no further studies are required, and the applicant provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, entecavir. Overview based on literature review is appropriate.

III.2 Pharmacology

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits the 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA.

The drug substance is a well-known compound. No further information was provided regarding the pharmacology of entecavir.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Published information on toxicological studies with entecavir was the basis for the evaluation. No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment

Since Nadcad 0.5 mg and 1 mg film-coated 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics, and toxicology of entecavir are well-known. As Tacluv 0.5 mg and 1 mg film-coated tablets are generic products, there is no need for further excessive non-clinical studies.

The non-clinical part of the application was acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of entecavir is well known.

Except for demonstrating bioequivalence no new non-clinical pharmacokinetic studies were conducted by the applicant as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Entecavir is rapidly absorbed with peak plasma concentrations occurring between 0.5-1.5 hours. The absolute bioavailability has not been determined. Based on urinary excretion of unchanged drug, the bioavailability has been estimated to be at least 70%. There is a dose- proportionate increase in C_{max} and AUC values following multiple doses ranging from 0.1-1 mg. The estimated volume of distribution for entecavir is in excess of total body water. Protein binding to human serum protein in vitro is ≈ 13%.

Entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system. Following administration of ^{14}C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide, and sulphate conjugates, were observed.

Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady-state of about 75% of the dose. Renal clearance is independent of dose and ranges between 360-471 ml/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion.

IV.2.2 Bioequivalence study

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

A pivotal bioequivalence study was performed. Its main objective was to compare the rate and extent of absorption of the Test- and Reference products administered to healthy volunteers in a single dose under fasting conditions. The Test product was Nadcad 1 mg film-coated tablet (PharOs Ltd., Greece) while the Reference product was Baraclude 1 mg film-coated tablet (Bristol-Myers Squibb EEIG). The investigation was a single-

dose, randomized, open-label, crossover, bioequivalence study in healthy adult subjects under fasting condition.

By the sponsor's statement the study was conducted in compliance with the requirements of *Guideline on Good Clinical Practice*, ICH Topic E6 (CPMP/ICH/135/95), and *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98) and ethical principles stated of the *Declaration of Helsinki* (Tokyo, 2004). The study sites of the bioequivalence study were inspected by EU authorities. These inspection completed with satisfactory results and conclusions.

The determination of entecavir in plasma samples was performed using an LC-MS/MS method.

The pharmacokinetic parameters calculated were as follows.

- primary: AUC_{0-72}, C_{max},
- other: AUC_{∞}, T_{max}, T_{half}, λ_z,.
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Descriptive statistics of pharmacokinetic parameters were arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for Test- and Reference pharmacokinetic data.

Bioequivalence criteria: the Test product can be considered bioequivalent to the Reference product, when the ln-transformed Test/Reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00% for entecavir.

The results are summarised below.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference %	Confidence intervals %	CV%
AUC_{0-72}	104.47	101.68 – 107.34	5.48
C_{max}	100.47	94.82 – 106.45	11.74

The results derived from analysis of log-transformed primary efficacy parameters (C_{max}, AUC_{0-72}) for entecavir show that the Test/Reference ratios of least-squares mean values and their 90% confidence intervals also are entirely included within the acceptance range of 80% - 125%. Thus, results support the bioequivalence between the Test- and Reference treatments.

Safety results: no death, serious or life-threatening adverse events occurred during the study. No new safety concern was identified.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 0.5 on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

- both strengths, i.e. 0.5 mg and 1 mg of proposed pharmaceutical products are manufactured by the same manufacturer using the same manufacturing procedure,
- the qualitative composition of the two claimed strengths is the same,
- the quantitative compositions of the claimed two strengths (0.5 mg and 1 mg) are proportionally similar,
- *in-vitro* dissolution data (covering the pH range of 1.2-6.8) confirm the in vivo similarity between the claimed strengths,
- pharmacokinetics of entecavir is linear in the claimed therapeutic range (0.5 - 1 mg).

The biowaiver claim for the 0.5 mg dose strength is acceptable.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence study Nadcad 1 mg film-coated tablets are considered bioequivalent with Baraclude 1 mg film-coated tablets (Bristol-Myers Squibb EEIG). The results of bioequivalence study with the 1 mg formulation can be extrapolated to the other strength 0.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of Tacluv 0,5 mg, 1 mg film-coated tablets, and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy profile of entecavir.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted, and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the safety profile of entecavir.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the Good Pharmacovigilance Practice module, the RMS considers the Summary acceptable.

IV.6.2 Risk Management Plan

The applicant has submitted a risk management plan (RMP), 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 Nadcad film-coated tablets.

The applicant has identified the following safety concerns in the RMP.

Table of safety concerns	
Important identified risks	Exacerbation of hepatitis. Entecavir resistance. Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment
Important potential risks	Carcinogenicity. Mitochondrial toxicity.
Missing information	Long-term safety and clinical outcomes data. Use in the paediatric population. Use in pregnancy. Use in elderly patients (≥ 65 years of age). Use in severe acute exacerbation of CHB.

The safety concerns listed by applicant are endorsed.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all safety concerns connected to Nadcad film-coated tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet, and classification as a prescription-only medicine) are considered sufficient to manage all safety concerns connected to Nadcad film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

With regard to Periodic Safety Update Report (PSUR) submission, the marketing authorisation holder should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lock Point and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the marketing authorisation holder should follow the Data Lock Points according to the EURD list.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on humans. For these applications, the bioequivalence studies described in section IV.2 are pivotal.

To support the application, the applicant has adequately demonstrated bioequivalence between entecavir test products and Baraclude® 0.5 mg and 15 mg film coated tablets.

There are no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Nadcad 0.5 mg, 1 mg film-coated tablets, generic versions of entacavir. The applicant and the future holder of authorisation is PharOs Pharmaceutical Oriented Services Ltd.

Tacluv 0,5 mg, 1 mg film coated tablets are 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.

To support the application the applicant has adequately demonstrated bioequivalence between Nadcad 0.5 mg and 1 mg film-coated tablets and Baraclude 0.5 mg and 1 mg film-coated tablet (Bristol-Myers Squibb EEIG) according to the bioequivalence guideline (CPMP/EWP/QWP/1401/98/rev 1/Corr**).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Nadcad 0.5 mg and 1 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IA 1.N Instead of ASMF a CEP procedure for specifying quality of the drug substance	HU/H/0482/001-002/IA/001	no	10. 07. 2019	03. 08. 2019	approved	no