Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Entecavir Sun 0.5 mg film-coated tablets
Entecavir Sun 1 mg film-coated tablets
(Entecavir monohydrate)

Procedure No: UK/H/6402/001-002/DC

UK Licence Number/s: PL 31750/0107-0108

Sun Pharmaceutical Industries Europe B.V.

Lay Summary
Entecavir Sun 0.5 and 1 mg film-coated tablets
(Entecavir monohydrate)

This is a summary of the Public Assessment Report (PAR) for Entecavir Sun 0.5 mg film-coated tablets and Entecavir Sun 1 mg film-coated tablets (PL 31750/0107-0108; UK/H/6402/001-002/DC). It explains how Entecavir Sun 0.5 mg film-coated tablets and Entecavir Sun 1 mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

The products will be collectively referred to as Entecavir tablets throughout the remainder of the PAR.

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

What are Entecavir tablets and what are they used for?
Entecavir tablets are 'generic medicines'. This means that Entecavir tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Baraclude 0.5 and 1 mg film-coated tablets (Bristol Myers Squibb Pharma EEIG; EU/1/06/343/001-003-006 and EU/1/06/343/004-007-002).

Entecavir tablets are anti-viral medicines, used to treat chronic (long term) hepatitis B virus (HBV) infection in adults. Entecavir 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 tablets are also used to treat chronic (long term) HBV infection in children and adolescents aged 2 years to less than 18 years. Entecavir 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 reduces the amount of virus in the body, and improves the condition of the liver.

How do Entecavir tablets work?
Entecavir tablets contain the active ingredient Entecavir monohydrate which belongs to nucleoside analogs. It works by decreasing the amount of hepatitis B virus (HBV) in the body.

How are Entecavir tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth). In most cases Entecavir tablets may be taken with or without food. However, if the patient has had previous treatment with a medicine containing the active substance lamivudine they should consider the following:

- If the patient was switched over to Entecavir tablets because the treatment with lamivudine was not successful, Entecavir tablets should be taken on an empty stomach once daily. If the liver disease is very advanced, the doctor will also instruct Entecavir tablets to be taken on an empty stomach. Empty stomach means at least 2 hours after a meal and at least 2 hours before your next meal.
- Children and adolescents (from 2 to less than 18 years of age) can take Entecavir tablets with or without food.

The patient's doctor will advise on the dose that is right for the patient. Always take the dose recommended by a doctor to ensure that the medicine is fully effective and to reduce the development of resistance to treatment. Patients must take Entecavir as long as the doctor has told them to. The doctor will tell them if and when they should stop the treatment.

The recommended dose in adults is either 0.5 mg or 1 mg once daily orally (by mouth).

The dose will depend on:

- whether patients have been treated for HBV infection before, and what medicine they received.
- whether patients have kidney problems. A doctor may prescribe a lower dose for or instruct them to take it less often than once a day.
- the condition of the liver

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 entecavir in children less than 2 years of age or weighing less than 10 kg. For children and adolescents (from 2 to less than 18 years of age), Entecavir 0.5 mg tablets are available or an entecavir oral solution may be available. All dosing will be taken once daily orally (by mouth).
- For children and adolescents weighing less than 32.6 kg and for dosages below 0.5 mg an entecavir oral solution may be available. The child's doctor will decide the right dose based on the child's weight.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Entecavir tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Entecavir tablets have been shown in studies?
Because Entecavir tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference products, Baraclude 0.5 mg and 1 mg film-coated tablets. 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 tablets?
Because Entecavir tablets are generic medicines and are bioequivalent to the reference medicines Baraclude 0.5 mg and 1 mg film-coated tablets their benefits and possible side effects are taken as being the same as those for the reference products.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Entecavir tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Entecavir tablets approved?
It was concluded that, in accordance with EU requirements, Entecavir tablets have been shown to have comparable quality and to be bioequivalent to Baraclude 0.5 mg and 1 mg film-coated tablets. Therefore, the MHRA decided that, as for Baraclude 0.5 mg and 1 mg film-coated tablets; the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Entecavir tablets?
A risk management plan (RMP) has been developed to ensure that Entecavir tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Entecavir 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.

Other information about Entecavir tablets
Germany, Italy, Poland, Romania, Spain, and the UK agreed to grant Marketing Authorisations for Entecavir tablets on 10 September 2018. Following a national phase, Marketing Authorisations were granted in the UK on 04 October 2018.

The full PAR for Entecavir tablets follows this summary.

This summary was last updated in November 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Entecavir Sun 0.5 mg film-coated tablets and Entecavir Sun 1 mg film-coated tablets (PL 31750/0107-0108; UK/H/6402/001-002/DC), are approvable. Entecavir tablets are Prescription-Only Medicines (POM) indicated for the treatment of chronic hepatitis B virus (HBV) infection (see section 5.1) 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 (see section 4.4).

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Italy, Poland, Romania, and Spain as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The applicant has cross-referred to Baraclude 0.5 mg and 1 mg film-coated tablets as the reference medicinal products, originally authorised to Bristol-Myers Squibb Pharma EEIG via the centralised procedure (EU/1/06/343/001,003,006 and EU/1/06/343/002,004,007) on 26 June 2006.

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 entecavir-TP Ki for HBV DNA polymerase is 0.0012 μM. Entecavir-TP is a weak inhibitor of cellular DNA polymerases α, β, and δ with K_i values of 18 to 40 μM. In addition, high exposures of entecavir had no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells (K_i > 160 μM).

A single open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, two-way crossover bioequivalence study conducted under fasting conditions was submitted to support these applications. The bioequivalence study is stated to have been conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a film coated tablet and each tablet contains 0.5 mg or 1 mg of entecavir (as entecavir monohydrate), as the active ingredient. Other ingredients consist of the pharmaceutical excipients as follows:
Tablet core; Lactose monohydrate (Pharmatose 200M), povidone K30, crospovidone, microcrystalline cellulose PH 102 and magnesium stearate.

Film coating for 0.5 mg, Opadry 13B58802 white contains: HPMC 2910/hypromellose (E464), titanium dioxide (E171), macrogol 400 (E1521) and polysorbate 80 (E433).

Film coating for 1 mg, Opadry 13B84610 pink contains: HPMC 2910/hypromellose (E464), titanium dioxide (E171), macrogol 400 (E1521), polysorbate 80 (E433) and iron oxide red (E172).

The finished product is presented in cold form unit dose blisters in pack sizes of 30 or 90 film-coated tablets in oriented polyamide, aluminium foil and polyvinyl chloride film (OPA/ALU/PVC) with a backing of hard tempered, aluminium foil coated with heat seal lacquer on inner side. The product is also presented in in high density polyethene (HDPE) bottles with 33mm neck finish and a Child Resistant closure with induction seal liner, available in pack sizes of 30 or 90 film-coated tablets. Each carton contains one bottle. Not all pack sizes may be marketed.

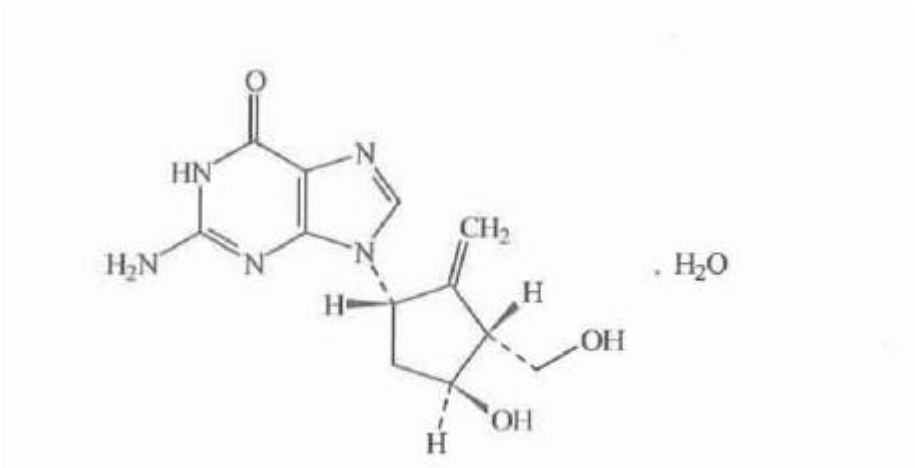
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Entecavir monohydrate

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

Structure:



Molecular formula: $C_{12}H_{15}N_5O_3.H_2O$

Molecular weight: 295.3

Appearance: A white or almost white powder.

Solubility: Practically insoluble in water, in anhydrous ethanol and in heptane, slightly soluble in methanol.

Entecavir monohydrate is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards used. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing 0.5 mg or 1 mg entecavir monohydrate that are generic versions of the reference products Baraclude 0.5 mg and 1 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film coating; Opadry white and Opadry pink which comply with in-house specifications and iron oxide red (E172) which complies with the national formulary. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable specifications and certificates of analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specifications
The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies, for all

packaging presentations support a shelf-life of 2 years for the unopened product with a in-use shelf life of 30 days. This medicinal product does not require any special temperature storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of entecavir monohydrate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

The impurities associated with the drug substance and drug product appear to be well controlled and within the limits set out in ICH guidelines and the Ph Eur monograph for entecavir monohydrate, therefore no toxicological qualification is necessary.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Entecavir tablets are 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

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of entecavir monohydrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of entecavir monohydrate.

Entecavir tablets can be considered bioequivalent to Baraclude 1 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG). The justification for the biowaiver of the 0.5 mg Tablet is acceptable.

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover comparative bioequivalence study of the applicant's test product Entecavir 1 mg

tablets (Sun Pharmaceutical Industries Europe B.V.) *versus* the reference product, Baraclude 1 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG) in healthy adult subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x1 mg tablet) of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 39 days.

Summary of pharmacokinetic results:

Product/Statistics	C_{max}* (pg/mL)	AUC_{0-72}* (Hr*pg/mL)
Test Product T		
Geometric Mean	9620.59	24747.5777
CV(%)	27.28	17.47
N	20	20
Reference Product R		
Geometric Mean	9330.44	24160.8648
CV(%)	24.68	18.23
N	20	20
Least squares mean		
T	9620.59	24747.5777
R	9330.44	24160.8648
Ratio of least squares mean		
T/R(%)	103.11	102.43
90% Confidence Intervals(T/R)		
Lower Limit:	92.06	100.05
Upper Limit:	115.48	104.87
p-value[ANOVA]		
Formulation	0.6450	0.0938
Period	0.7006	0.7306
Sequence	0.3544	0.2917
Power (%)	89.72	100.00
Intra-subject CV(%)	20.89	4.29

*** Log-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported**

Parameter	Entecavir Test (T) vs. Reference (R)
ln C_{max}	103.11% (92.06% – 115.48%)
ln AUC_{0-72}	102.43% (100.05% – 104.87%)

Study conclusion

The 90% confidence intervals of the test/reference ratio for AUC_{0-t} and C_{max} values lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of

Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Baraclude 1 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG).

As the 0.5 mg and 1 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 1 mg tablet strength can be extrapolated to the 0.5 mg strength tablet.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) 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 Entecavir tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Summary 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	• Mitochondrial toxicity
Missing information	• Use in the paediatric population • Use in pregnancy and lactation • Use in elderly patients (≥ 65 years of age) • Use in severe acute exacerbation of chronic hepatitis B

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

V 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 PIL 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.

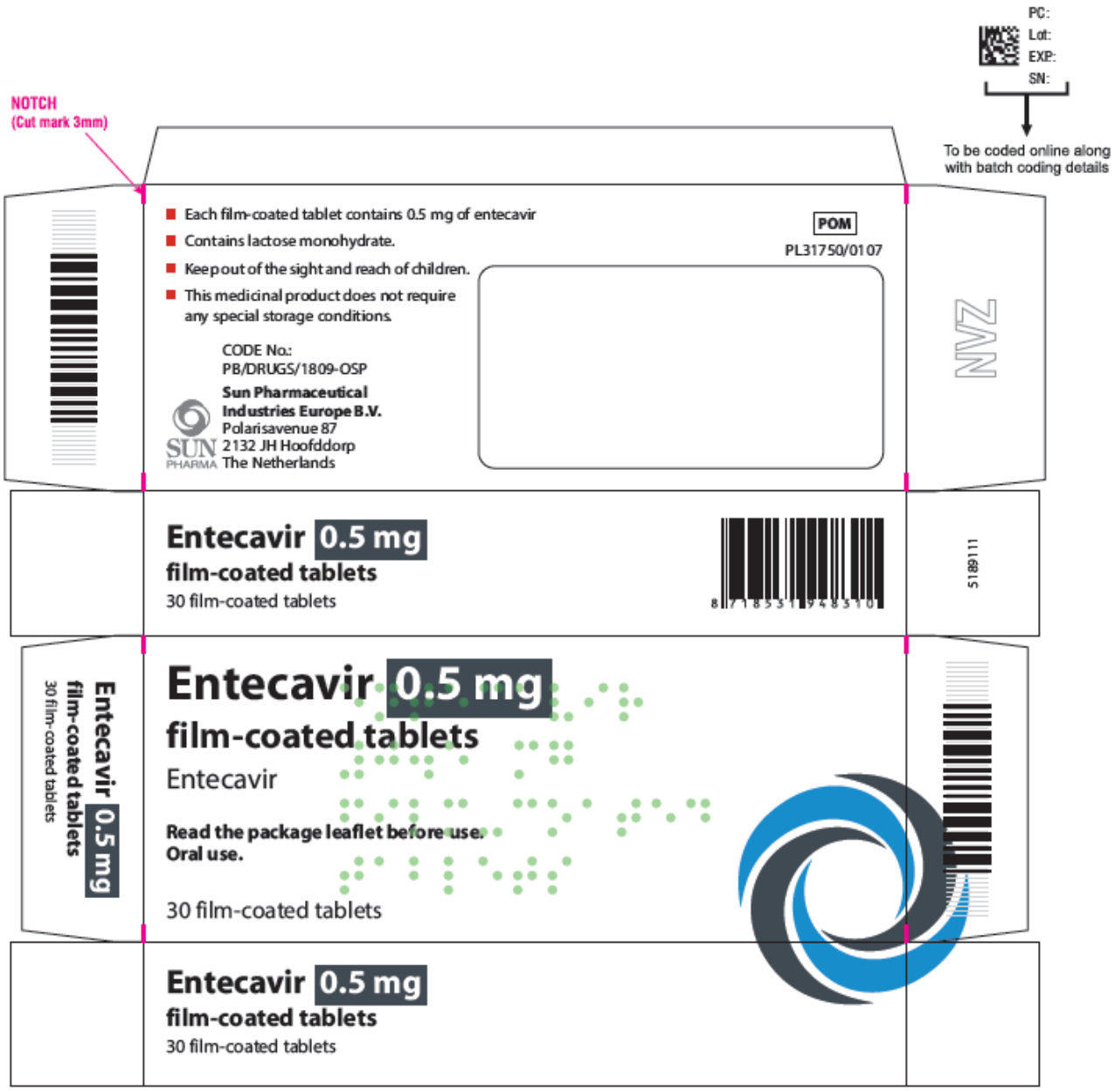
VI Overall conclusion, benefit/risk assessment and recommendation

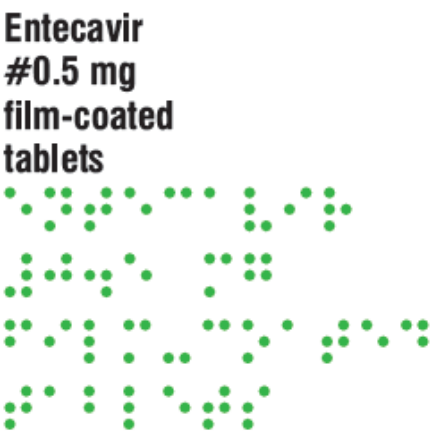
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with entecavir monohydrate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.

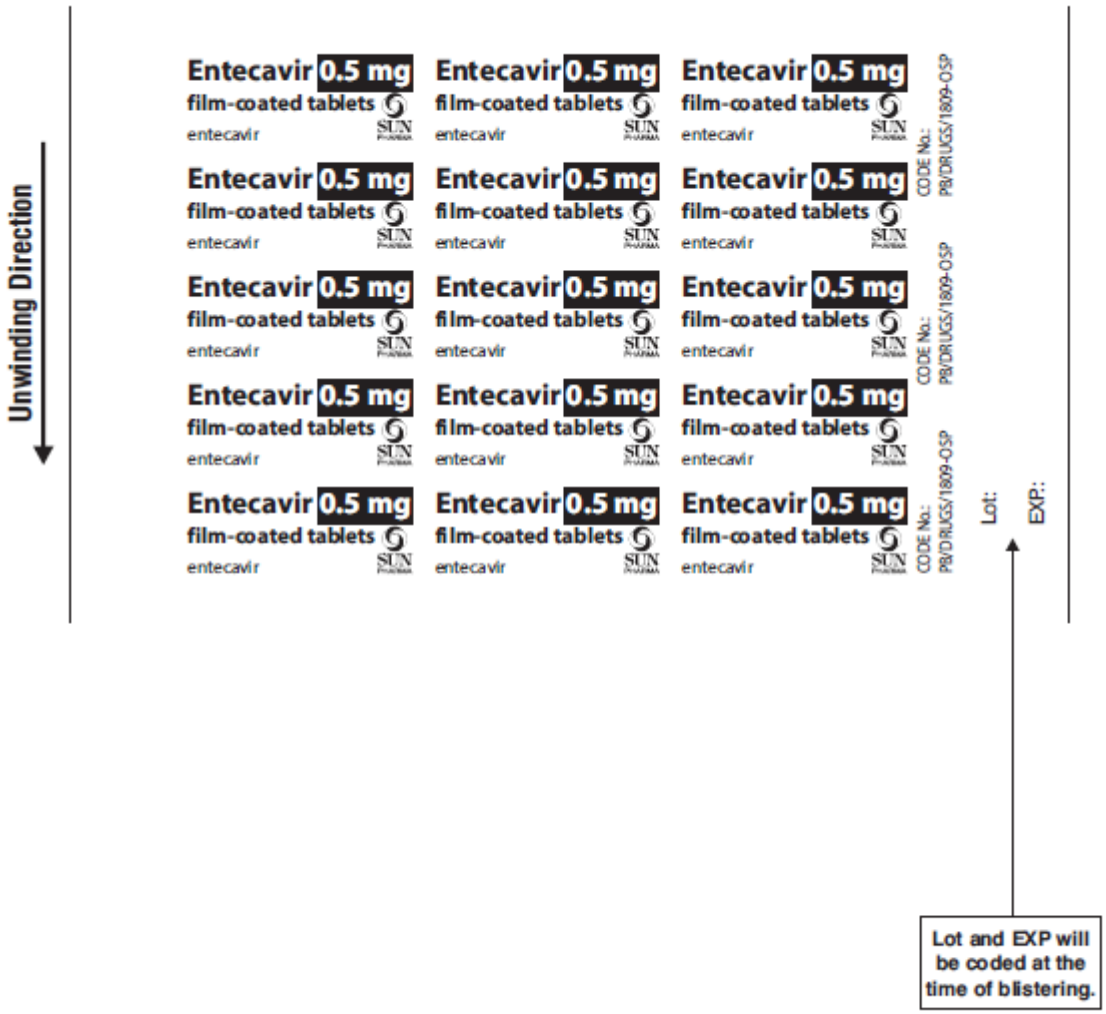
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

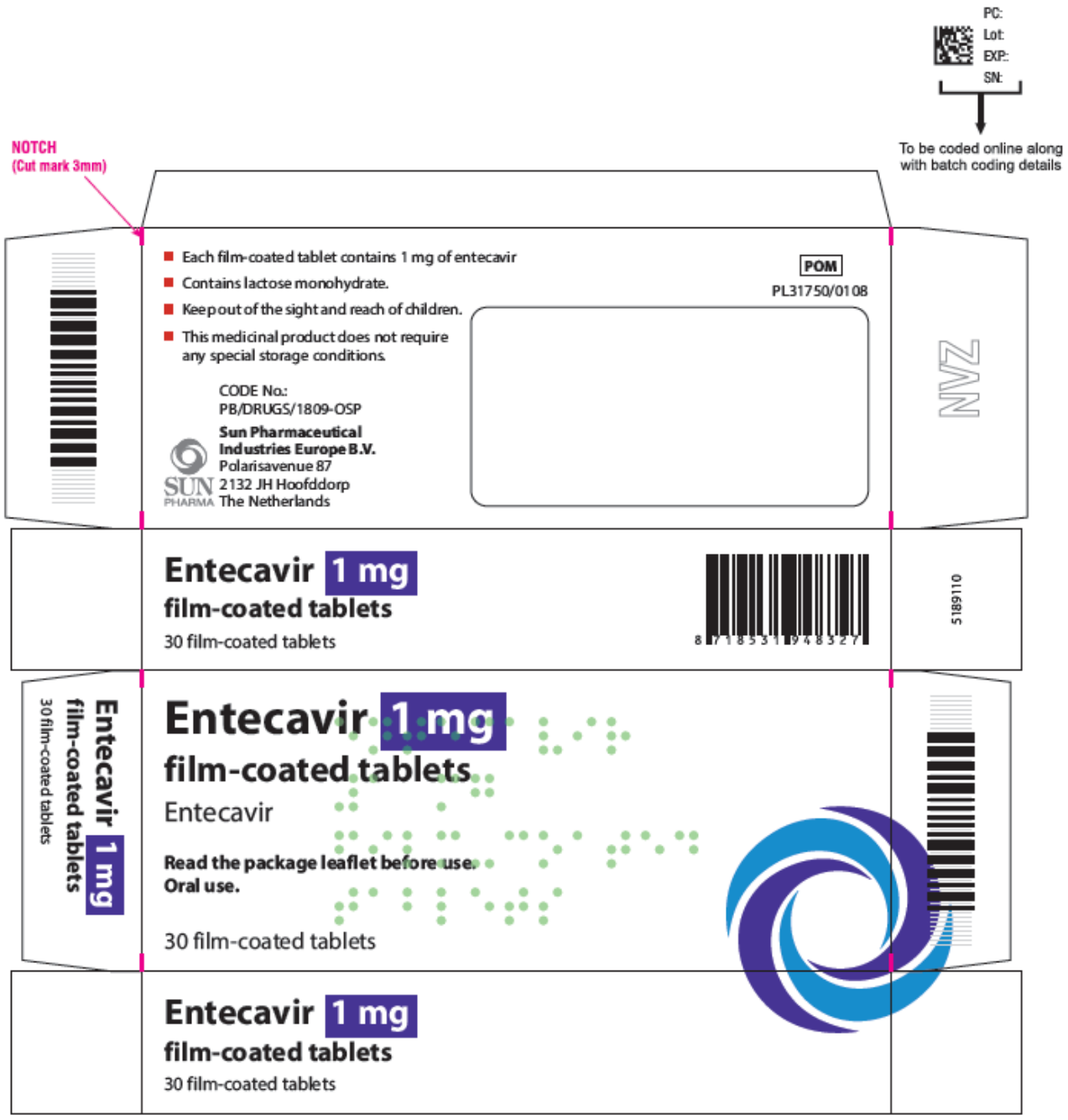
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

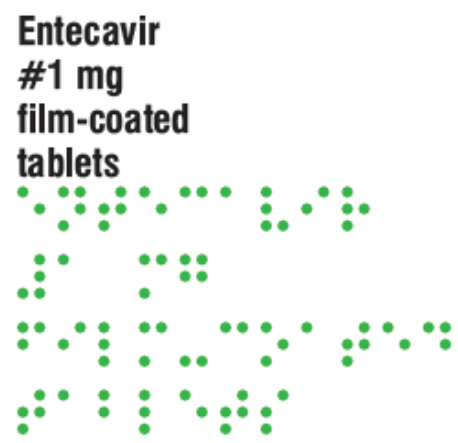
The approved labelling for this medicine is presented below:

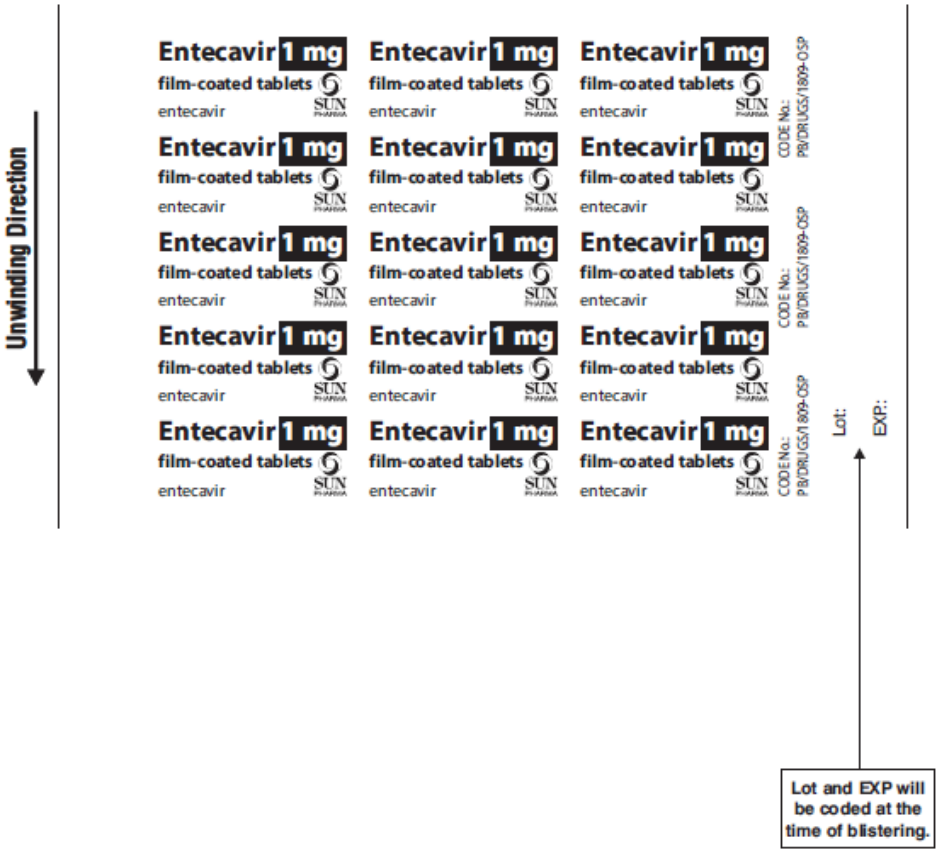

PC:
Lot:
EXP:
SN:
To be coded online along with batch coding details
NOTCH
(Cut mark 3mm)
Each film-coated tablet contains 0.5 mg of entecavir
Contains lactose monohydrate.
Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
POM
PL31750/0107
CODE No.:
PB/DRUGS/1809-OSP
Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands
SUN PHARMA
NVZ
Entecavir 0.5 mg
film-coated tablets
30 film-coated tablets
5189111
Entecavir 0.5 mg
film-coated tablets
30 film-coated tablets
Entecavir 0.5 mg
film-coated tablets
Entecavir
Read the package leaflet before use.
Oral use.
30 film-coated tablets
Entecavir 0.5 mg
film-coated tablets
30 film-coated tablets


Entecavir
#0.5 mg
film-coated
tablets


Unwinding Direction
Entecavir 0.5 mg
film-coated tablets
entecavir
SUN PHARMA
CODE No.: PB/DRUGS/1809-OSP
Lot:
EXP.:
Lot and EXP will be coded at the time of blistering.


PC:
Lot:
EXP:
SN:
To be coded online along with batch coding details
NOTCH
(Cut mark 3mm)
Each film-coated tablet contains 1 mg of entecavir
Contains lactose monohydrate.
Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
POM
PL31750/0108
CODE No.:
PB/DRUGS/1809-OSP
Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands
NVZ
Entecavir 1 mg
film-coated tablets
30 film-coated tablets
8 718531 948327
5189110
Entecavir 1 mg
film-coated tablets
30 film-coated tablets
Entecavir 1 mg
film-coated tablets
Entecavir
Read the package leaflet before use.
Oral use.
30 film-coated tablets
Entecavir 1 mg
film-coated tablets
30 film-coated tablets


Entecavir
#1 mg
film-coated
tablets


Unwinding Direction
Entecavir 1 mg
film-coated tablets
entecavir
SUN PHARMA
CODE No: PB/DRUGS/1809-OSP
Lot:
EXP:
Lot and EXP will be coded at the time of blistering.

Annex 1

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)