20 July 2017
EMA/555410/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entecavir Mylan

International non-proprietary name: entecavir

Procedure No. EMEA/H/C/004377/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Events
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File = Drug Master File
AUC	Area under curve
AUC ratio	The ratio of AUC0-t to AUC0-∞ expressed in (%) percentage
AUC0-72	The area under the plasma concentration versus time curve from time 0 to 72 hours
AUC0-∞	The area under the plasma concentration versus time curve from time 0 to infinity
AUC0-t	The area under Plasma concentration versus time curve from time 0 to t, where t = time of last measurable concentration
CFU	Colony Forming Units
Cmax	Peak plasma concentration
CV	Coefficient of Variation
CHMP	Committee for Medicinal Products for Human use ERA Environmental Risk Assessment
ETV	Entecavir monohydrate
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of
IR	Infrared
KETE	(1*S*,*2R*,3*S*,5*R*)-3-(benzyloxy)-2-(benzyl oxymethyl)-6-oxabicyclo[3.1.0]hexane (also called NTKW-3)
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOQ	Limit of quantitation
LQCT	Last measurable blood sampling point
LSM	Least Square Mean
MAH	Marketing Authorisation Holder
mg	Milligram
min	Minute
Ml	Milliliter
MS	Mass Spectrometry
NTKW-3	(1*S*,*2R*,3*S*,5*R*)-3-(benzyloxy)-2-(benzyl oxymethyl)-6-oxabicyclo[3.1.0]hexane (also called KETE)
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OPA	Orientated polyamide
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK/PD	Pharmacokinetics/Pharmacodynamics
PXRD	Powder X-ray difraction
PVC	Poly vinyl chloride
RH	Relative Humidity
SAS	Statistical Analysis Software
SmPC, SPC	Summary of Product Characteristics
T1/2	Half-life
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis

TLC	Thin layer chromatography
TLIN	Time point at which log linear elimination begins
Tmax	Time of the maximum measured plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	ultra-high performance liquid chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 29 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Entecavir Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 January 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Entecavir Mylan is 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)

For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B, see sections 4.2, 4.4 and 5.1.

Entecavir Mylan 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. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, and 5.1."

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Baraclude instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Baraclude, 0.5 mg and 1 mg, Film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG

- Date of authorisation:26-06-2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/001-004 and EU/1/06/343/006-007

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Baraclude, 0.5 mg and 1 mg, Film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation:26-06-2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/001-004 and EU/1/06/343/006-007

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Baraclude, 0.5 mg and 1 mg, Film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26-06-2006
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/06/343/001-004 and EU/1/06/343/006-007

Bioavailability study number(s): study 318-13 conducted with the 1 mg strength and a biowaiver for the 0.5 mg was acceptable.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alexandre Moreau

- The application was received by the EMA on 29 June 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 15 November 2016.
- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 February 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 April 2017.
- During the PRAC meeting on 5 May 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 18 May 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 June 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Entecavir Mylan.

2. Scientific discussion

2.1. Introduction

The application for entecavir Mylan was submitted by MYLAN S.A.S, via the centralised procedure as a Generic of a Centrally Authorised Medicinal Product of Regulation (EC) No 726/2004 and according to Article 10(1) generic application of Directive 2001/83/EC. Entecavir Mylan is a generic version of the already approved reference product Baraclude 0.5 mg film-coated tablet, authorized on 26 June 2006 (marketing authorisation numbers EU/1/06/343/003, EU/1/06/343/006 and EU/1/06/343/001) and to Baraclude 1 mg film-coated tablet, authorized on 26 June 2006 (marketing authorisation numbers EU/1/06/343/004, EU/1/06/343/007 and EU/1/06/343/002).

Entecavir is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) polymerase. After phosphorylation to the tri-phosphate (TP) form, entecavir-TP, by competing with the natural substrate deoxyguanosine 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. In conclusion, entecavir inhibits HBV DNA synthesis.

The applicant submitted one bioequivalence study conducted with Entecavir Mylan 1 mg, and a biowaiver for the 0.5 mg was claimed.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 0.5 mg and 1 mg of entecavir (as monohydrate) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, crospovidone, lactose monohydrate and magnesium stearate.

Tablet coating: titanium dioxide (E171), hypromellose, macrogol and polysorbate 80.

The product is available in OPA/Aluminium/PVC-Aluminium foil blister packs or high density polyethylene (HDPE) bottle with child-resistant polypropylene closure as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

Entecavir monohydrate is an established active substance described in the European Pharmacopoeia (Ph Eur). The chemical name of entecavir monohydrate is 2-amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxylmethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one, monohydrate corresponding to the molecular formula $C_{12}H_{15}N_5O_3 \cdot H_2O$ and has a relative molecular mass 295.29 g/mol and has the following structure:

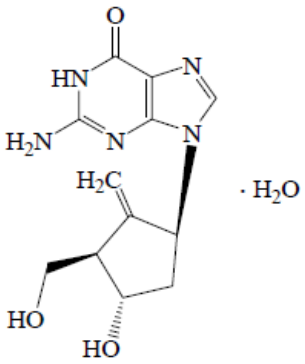

Figure 1. Structural formula of entecavir monohydrate

The structure of Entecavir has been confirmed by various analytical and spectral techniques. These included: elemental (C, H, N) analysis, thermal analysis, UV spectroscopy, IR spectroscopy ^{1}H—NMR, ^{13}C – NMR, 2D ^{1}H-^{1}H ^{1}H-^{13}C COSY NMR and mass spectrometry studies.

The TGA analysis showed that the active substance contains one molecule of crystal water.
The stereochemistry of active substance is proven by X-ray analysis of a single crystal.

The active substance is a white or almost white crystalline powder. It is sparingly soluble in *N, N*-dimethylformamide, slightly soluble in methanol and in ethanol (99.5); practically insoluble in acetonitrile, very slightly soluble in water.

Entecavir exhibits stereoisomerism due to the presence of three chiral centres. The compound is optically enantiomerically pure with a relative configuration of (C1 *S*, C3 *R*, C4 *S*). The stereochemistry originates from the starting material NTKW-3. Enantiomeric purity is controlled routinely by specific optical rotation in the specifications.

Entecavir monohydrate exhibits polymorphism. It exists in several crystalline forms and an amorphous form.

It was confirmed by the ASMF holder that the active substance consistently produced by the proposed manufacturing process is the selected crystalline form. This was supported with data on 3 consecutives batches of active substance from the proposed manufacturer. In addition, a test for polymorphic form is included the specification of the active substance. As indicated in the stability section, it has also been demonstrated that the polymorphic form is stable under storage.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesized in seven linear stages which comprise 5 chemical transformations, using well defined starting materials with acceptable specifications, and 2 purification steps.

Following a major objection from the CHMP, the active substance starting materials were redefined to an earlier step in the synthesis of entecavir monohydrate during the evaluation procedure. The originally proposed active substance starting material the protected form of entecavir and the number of chemical transformation steps conducted under GMP was considered insufficient (e.g. did not include the formation of asymmetric centres) to guarantee the quality of the active substance. According to the batch analysis data presented, the assay specification limit for one of the re-defined and accepted starting materials could be improved. Since this has no impact on the benefit/risk of the product, the applicant is recommended to further study and justify this limit, or tighten it.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The quality of the starting material, solvents, reagents are acceptable for their intended use.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Following the redefinition of the starting material, the active substance manufacturer performed an analysis on potential genotoxic or mutagenic impurities on the raw materials, reagents used in the manufacturing

process along with the intermediates and the potential impurities. It was concluded that five genotoxic impurities are likely to be formed during the synthesis of Entecavir monohydrate. Based on the maximum daily dose of 1 mg for Entecavir and the TTC value of 1.5 µg/day specified in the Guideline on the limits of genotoxic impurities (EMEA/CHMP /QWP /251344 /2006) the active substance manufacturer established a limit for these impurities. This was considered satisfactory.

The active substance is packaged in double low density polyethylene (PE) bags. The bags are sealed by heat and put into aluminum tin. The PE bags comply with Directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), solubility (Ph. Eur.), identification (specific optical rotation, IR absorption), specific optical rotation (Ph. Eur.), water content (KF), sulfated ash (Ph. Eur.), impurity F (Ph. Eur.), related substances (HPLC) (Ph. Eur.), assay (HPLC) (Ph. Eur.), residual solvents (GC), polymorphic form (PXRD), microbial enumeration tests (TAMC, TYMC) (Ph. Eur.) and benzyl chloride (GC).

The specification was established based on the Ph. Eur. monograph for entecavir monohydrate. The proposed limits are in line with the current Ph. Eur. monograph and ICH Q3C guideline.

A test for polymorph form was added to the active substance specification following a request from CHMP during the evaluation, since the active substance is very slightly soluble in water.

The absence of a test for heavy metals and elemental impurities, used as catalysts in the synthesis of the active substance, has been justified based batch analysis data from 7 batches of entecavir monohydrate which showed low levels and data from three commercial scale batches of active substance where these impurities were not detected, respectively. This was considered acceptable.

The absence of routine control for other solvents was also justified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for system suitability and entecavir monohydrate impurity F has been presented.

Batch analysis data from three commercial scale of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on four commercial scale batches of active substance from the proposed manufacturer stored in a container closure system similar to that intended for the market (PE bags) for 36 months under long term conditions at 25±2 ºC / 60±5% RH and for up to 6 months under accelerated conditions at 40±2 ºC / 75%±5 RH, according to the ICH guidelines, were provided.

The following parameters were tested*:* appearance, identification, specific optical rotation, water, impurity F, related substances, assay, sulfated ash, residual organic solvent and microbial limits. The analytical methods used were the same as for release and were stability indicating.

Al results were within the specification and no trend of degradation was observed under long term or accelerated conditions.

In addition, the active substance manufacturer performed the polymorphism (PXRD) test on Entecavir samples stored under the long term stability conditions at the initial and 36 month time points. The results demonstrated that the produced polymorphic form is stable under storage.

Moreover, in order to assess risk of conversion of entecavir active substance crystalline form ~~1~~ stress studies under exposure to moisture, high temperature/high humidity and high temperature were conducted. An aqueous granulated sample was also placed at high temperature/high humidity and high temperature. No change in active substance polymorph was observed in any sample.

Results on stress conditions including light exposure, high temperature, acidity, alkali and oxidation showed that entecavir is not degraded under light exposure and acid, slightly degraded under high temperature, strongly degraded under alkali and oxidation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored protected from light in the proposed container (double polyethylene bag placed in an aluminium tin).

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product Entecavir Mylan consists of film-coated tablets available in two strengths:

Entecavir 0.5 mg film-coated tablets:
White, film-coated, round, biconvex, bevelled edge tablet debossed with 'M' on one side of the tablet and 'EA on the other side.
Diameter: Approximately 6.8 mm

Entecavir 1 mg film-coated tablets:
White, film-coated, round, biconvex, bevelled edge tablet debossed with 'M' on one side of the tablet and 'EB' on the other side.
Diameter: Approximately 8.8 mm

Visually, the two strengths differ in tablet size, weight and embossed inscription.

The purpose of the pharmaceutical development studies was to develop stable entecavir immediate release film-coated tablets bioequivalent to the reference medicinal product Baraclude film-coated tablets (Bristol-Myers Squibb Pharma EEIG) marketed in Europe, using commonly used excipients and similar to the reference product.

No oral solution was developed by the applicant. Since the tablets can be delivered to children between 2-6 years, further information about administration to paediatric population including a reference to the alternative pharmaceutical form (oral solution) available for the reference product have been introduced in the SmPC.

The formulation of Entecavir film-coated tablets is based on the literature search and characterization of reference product.

As indicated above, entecavir is a white or almost white crystalline powder. Bulk density, tapped density and compressibility index studies showed that the flowability of entecavir is poor. In order to overcome this and

given the low concentration of active substance in the formulation, which may cause content uniformity problem, a wet granulation was pursued. Since the manufacturing process of Entecavir film-coated tablets includes the dissolution of the active substance in purified water, the particle size of the active substance has no influence on the release characteristics of the product and no specifications are proposed.

A drug-excipient compatibility study was performed based on the qualitative formula of the reference product (binary mixtures exposed to high temperature/high humidity). The active substance was found compatible with all excipients tested.

Different concentrations of filler, diluent, disintegrant, lubricant, coating agent (lactose, microcrystalline cellulose PH101 and PH102, crospovidone) were studied. Based on results of average weight of tablets, hardness, thickness, friability, disintegration time and dissolution profile the formulation was optimized.

Qualitative compositions of the generic and reference medicinal products are very similar apart the generic product does not contain any povidone.

All excipients used for the finished product are conventional pharmaceutical ingredients that comply with the requirements of European Pharmacopoeia with the exception of film coating agent Opadry White used for the film coating which has in-house ~~specification. The~~ individual compendial components used for the manufacture of Opadry coating material comply with the Ph. Eur. monograph. The colorants used in Opadry coating material comply with EU Regulation 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

A single bioequivalence study No 318-13 was conducted for the 1 mg tablets in fasting state in healthy volunteers. Comparative dissolution profiles of the test and reference biobatches were generated in different dissolution media i.e. pH 1.2 HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer (release media) covering the pH range of pH 1.2 - pH 6.8 (apparatus II, 50 rpm, 1000ml). More than 85% of the labelled amount of the drug was released within 15 minutes from both test and reference batches used in bioequivalence study in all the three mediums. Hence, the dissolution profiles were considered similar.

A biowaiver was applied for the 0.5 mg strength in line with in CPMP guideline on the investigation of bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 – January 2010. From the quality point of view, the bio-equivalence study results of Entecavir Mylan 1 mg film-coated tablets can be extended to Entecavir Mylan 0.5 mg film-coated tablets since the 0.5 mg tablets are manufactured using the same manufacturing process at the same manufacturing site as the 1 mg tablets, their qualitative composition is identical, excipients are not expected to have interaction with the pharmacokinetics, and their quantitative formulations are proportional. In addition, both strengths exhibit comparable dissolution profiles *in vitro*. More than 85% of the labelled amount of the drug is released within 15 minutes from both 0.5mg and 1mg tablets (biobatch) in pH 1.2, 4.5 and 6.8 dissolution media.

The dissolution method development explored the use of different media, different agitation speeds and different media volumes. Paddle apparatus with a rotation speed 50 rpm was selected. Three physiological medium were tested: the drug dissolution profiles in all the three different dissolution media using 1000ml or 500ml (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) were found to be similar and complete (more than 85% of the labelled amount of drug is released within 15 minutes). pH 6.8 was selected and it was confirmed that the sink conditions are met.

The discriminatory power of the selected dissolution method was evaluated on batches manufactured varying the composition of the formulation or manufacturing process. The applicant concluded that the selected

dissolution medium is able to discriminate between the process change as well as the formulation change. Although the discriminatory power of the method should have been demonstrated by changing critical parameters which may affect dissolution and which may be encountered during routine manufacture, considering the very rapid dissolution in all physiological pH, it is assumed that changes in quantitative formulation or manufacturing parameters will not be detected and the method proposed is considered acceptable.

Comparative impurity profiles of the generic product Entecavir Mylan 0.5mg and 1mg film-coated tablets and the reference product Baraclude 0.5mg and 1mg of Bristol-Myers Squibb Pharma EEIG have been performed using the validated analytical method for related substances. Results showed that the level of total impurities is very low for the proposed finished product. Results are in compliance with the finished product shelf life specification.

The development of the manufacturing process of Entecavir film-coated tablets has been described in detail. It focused on the following process variables: drug solution preparation, fluid uptake, drying conditions, milling, blending times, tablet hardness.

The container closure systems proposed for marketing are a blister pack of cold laminate (OPA/Aluminium/PVC-Aluminium) in an outer cardboard carton, and a high density polyethylene (HDPE) bottle pack (white HPDE bottle with a child resistant white opaque polypropylene (PP) closure with aluminium induction sealing liner wad) placed in an outer carton.

Bulk packs are proposed for holding the finished product before packaging or for transportation to any other approved re-packaging site in Europe. Bulk pack consists in a low density polyethylene (LDPE) bag and placed in an outer triple laminated bag along with desiccant in between those bags and sealed. The triple laminated bags are then placed in a suitable tertiary pack.

A copy of certificate of analysis along with EC directive compliance/food grade certificates or conformity to the Ph. Eur. are provided for all the packaging materials. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the lactose monohydrate used in the finished product is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.
No other excipients derived from animal or human origin have been used.
Valid TSE CEPs from the suppliers of the excipients have been provided.

Manufacture of the product

The manufacturing process consists of eight main steps: dispensing, sifting, wet granulation, drying, sifting and milling, blending, compression, film-coating and packaging.

The common blend can be used to produce a single strength or can be subdivided to produce the two strengths.

Holding time studies were presented on one pilot scale intermediate lubricated blend, divided in two pilot batches of uncoated and film-coated tablets per strength. The data report showed that results of holding time studies carried out were satisfactory and within the predetermined specification limits.

The manufacturing process has been validated on 3 common blend batches which were further subdivided to manufacture one batch of Entecavir 0.5 mg film-coated tablets and one batch of Entecavir 1 mg film-coated tablets. Considering the low content of the active substance in the formulation the process should be considered as a non-standard one and validation results should have been presented on full scale batches before approval. However, given that the active substance is introduced dissolved in the granulation solution, the low content of active substance in the formulation is not a critical aspect. Therefore, the presented validation data on the lower proposed commercial batch size (which is also the pilot batch size) is considered sufficient. The validation protocol was updated to ensure additional controls i.e. increased sampling frequency and larger sample size in order to control the content uniformity of the tablets along the compression step.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual inspection), identification (HPLC, TLC), color identification of titanium dioxide (by chemical reaction), dissolution (HPLC), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF), microbial enumeration tests (TAMC, TYMC) and E. coli (Ph Eur).

The specifications cover appropriate parameters for this dosage form. All limits are in line with the requirements of ICH guidelines and the Ph. Eur. requirements.
In compliance with ICH Q3D guideline, the applicant performed the risk assessment of elemental impurities in Entecavir film-coated tablets. Based on the information provided, the omission of elemental impurities from the finished product specification is justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the active substance and impurities testing has been presented.

Batch analysis results are provided for three pilot scale (also minimum commercial scale) batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies were conducted on three pilot scale batches of each strength stored for 36 months under long term (25°C/60% RH) and 6 months under accelerated (40°C/75% RH) ICH storage conditions. The batches are representative to those proposed for marketing and were packed in the primary packagings representative of those proposed for marketing i.e. blister pack (OPA/Aluminium/PVC-Aluminium) and HDPE

bottle pack with a screw closure (instead of theHDPE bottle with a child resistant closure proposed for marketing).

Comparative moisture permeability (water-vapour transmission) data on HDPE bottle containers in line with the current edition of the USP <671> test for containers – permeation (multi-unit containers) were provided. The results demonstrated equivalent moisture protection between the two bottle configurations. The proposed child-resistant closure has the same induction sealing liner as that of the existing screw closure, which is in contact with the tablets. The bottles have the same neck size/type of closure, and the bottle remains unchanged (HDPE). Based on this information, it was concluded that the stability data on the bottle pack with screw closure are representative to the bottle pack with child-resistant closure.

A simulated bulk shipment pack, which only differs in dimensions with respect to the bulk pack, was also studied (12 months data).

In-use stability studies were performed on two batches of Entecavir 0.5 mg and 1 mg tablets in 90's HDPE bottle pack in compliance with the CPMP guidance – "Note for guidance on in-use stability testing of human medicinal products" (CPMP/QWP/2934/99).

A photo stability study was performed on Entecavir 1 mg film-coated tablets per ICH Q1B guideline.

Batches were tested for the following stability parameters: description, assay, related substances, dissolution, water content and microbial testing. The provided stability results are within the specifications set. The analytical procedures used are stability indicating.

All results complied with the proposed specification. No trends were observed in any of the parameters tested. Based on these results, it was concluded that Entecavir Mylan film-coated tablets are not photosensitive.

The proposed shelf-life of 12 months for the finished product packed in bulk shipment pack can be accepted.

Based on stability data presented, the proposed shelf life of 36 months for the finished product packed in blister pack (OPA/Aluminium/PVC-Aluminium) and HDPE bottle pack with a child resistant closure without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Nevertheless, as discussed above, according to the batch analysis data presented the assay specification limit for NTKW-3 could be improved. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-The applicant is recommended to further study and justify the current specification of one of the redefined starting materials. Otherwise, the assay specification limit should be tightened to an acceptable level.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the entecavir Mylan SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Entecavir manufactured by Mylan S.A.S is considered unlikely to result in any significant increase in the combined sales volumes for all entecavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased. CHMP agreed to this conclusion.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. This overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Entecavir Mylan was provided. The non-clinical data for entecavir is well known and thus new non-clinical data are not required. The non-clinical aspects of the entecavir Mylan SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing entecavir. To support the marketing authorisation application the applicant conducted one bioequivalence study with an open-label, balanced, randomized, two-

treatment, single-period, parallel, single dose design under fasting conditions. This study was the pivotal study of this application.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant submitted one bioequivalence study conducted with Entecavir Mylan 1 mg strength, and a biowaiver for the 0.5 mg was claimed.

According to the applicant, Entecavir 0.5 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies, as:

- both strengths of Entecavir 0.5 mg and 1 mg film-coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- The qualitative composition of both strengths is the same. Both strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths.
- The absorption kinetics of Entecavir is linear within the therapeutic dose range. The Applicant has therefore performed the bio-equivalence study with the 1 mg strength and extended the in-vivo performance to 0.5 mg strength.

Both strengths exhibit similar in-vitro performance and the dissolution profiles can be considered similar.

The 0.5 mg strength of Entecavir film-coated tablets fulfils the requirements to waive bioequivalence studies for additional strengths in accordance with the CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 – January 2010. As a consequence, the bio-equivalence study results of Entecavir 1 mg film-coated tablets can be extended to Entecavir 0.5 mg film-coated tablets.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, Study 318-13.

Table 1. Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study Status; Type of report
BA	Not Applicable								
BE	318-13	Module 5, Section 5.3.1.2	To compare the rate and extent of absorption of Entecavir 1 mg film-coated tablets (Test) manufactured by Mylan Laboratories Limited, India with that of Baraclude® 1 mg Comprimés Pelliculés (Reference) of Bristol-Myers Squibb Pharma EEIG. To monitor the adverse events and to ensure the safety of the subjects.	An open-label, balanced, randomized, two-treatment, single-period, parallel, single dose, comparative oral bioavailability study of Entecavir 1 mg film-coated tablets (Test) (manufactured by Mylan Laboratories Limited, India) and Baraclude® 1 mg Comprimés Pelliculés (Reference) of Bristol-Myers Squibb Pharma EEIG in healthy, adult, human subjects under fasting conditions.	**Reference Product:** Baraclude® 1 mg Comprimés Pelliculés Lot No.: 2K72364; Oral **Test Product:** Entecavir 1 mg film-coated tablets Batch No.: 2002693; Oral	~~Planned-60~~ Enrolled-60 Completed-60 Analyzed-60 Withdrawn-Nil	Healthy adult human subjects	Single dose	Complete; abbreviated
PK	Not Applicable								
PD	Not Applicable								
Efficacy	Not Applicable								

2.4.2. Pharmacokinetics

Study 318-13: An open-label, balanced, randomized, two-treatment, single-period, parallel, single dose, comparative oral bioavailability study of Entecavir 1 mg Film-coated Tablets (Test) of Mylan Laboratories Limited, India and Baraclude® 1 mg Film-coated Tablets (Reference) of Bristol-Myers Squibb Pharma EEIG in healthy, adult, human subjects under fasting conditions.

Methods

Study design

The study was a single-dose, open-label, laboratory-blinded, two-treatment, randomized, balanced, single-period oral bioequivalence study, with a parallel design, conducted on healthy volunteers under fasting conditions.

Clinical study centre: Axis Clinicals Limited, 1-121/1, Miyapur, Hyderabad-500 049, India.

Principal investigator: Dr.M.Gyaneshwar

Analytical study centre: Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No 4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A. S.Rao, Nagar, Hyderabad-500 062, India.

Pharmacokinetic and Statistical study centre: Axis Clinicals Limited, 1-121/1, Miyapur, Hyderabad-500 049, India.

Subjects were maintained an overnight fast of approximately 11 hours before dosing and a minimum of 4.0 hours thereafter. Subjects were allowed to leave the clinical facility at 48 h post-dose. Hence, the last sample (72 h) was ambulatory.

Test and reference products

Details	Reference Product (B)	Test Product (A)
Generic Name	Entecavir	Entecavir
Trade Name	Baraclude®	Not Available
Dosage form	Tablets	Tablets
Manufactured by	BRISTOL-MYERS SQUIBB PHARMA EEIG,Uxbridge Business Park,Sanderson Road,Uxbridge UB8 1 DH,Royaume-Uni	Mylan Laboratories Limited, F- 4& F-12,MIDC,Malegoan, Sinnar,Nashik-422 113, Maharashtra,India.
Dose	1 mg	1 mg
Lot	2K72364	-
Batch No	-	2002693
Manufacturing date	Not Available	MAR 2013

Population studied

A sample size of 30 subjects was considered for each treatment. Hence, the total sample size for two treatments was 60 subjects.

Volunteers aged from 18-45 years with a body mass index (BMI) of 18.5 -30 kg/m2 were selected according to the inclusion and exclusion criteria. They were assessed to be in healthy condition based on pre-study medical examination and laboratory tests (including serum creatinine, serum urea and serum uric acid); serum values and demographic data were presented separately for the two parallel arms in order to ensure comparability between groups.

All subjects completed the study.

Analytical methods

A method validation report was provided with satisfactory results.

Results for the incurred sample reanalysis are acceptable.

The long-term stability of entecavir in K_3EDTA plasma was established at -70 °C and -20°C for 87 days (data provided during the evaluation). This covers the maximal study sample duration storage of 52 days.

Pharmacokinetic variables

The following pharmacokinetic parameters were calculated using WinNonlin Professional Software Version 5.0.1 (Pharsight Corporation, USA): T_{max}, C_{max}, AUC_{0-72h}, kel and t1/2 for Entecavir. C_{max}, and AUC_{0-72h} were the primary pharmacokinetic parameters.

Statistical methods

Summary statistics were performed for both primary and secondary pharmacokinetic parameters.

The ratio of geometric least squares means, 90% confidence interval and inter-subject CV (%) were reported for Ln-transformed Cmax and AUC_{0-72h}.

Analysis of variance (ANOVA) was carried out by employing PROC GLM of SAS® release 9.1.3 (SAS Institute Inc., USA) for un-transformed and Ln-transformed Cmax and AUC_{0-72h} for Entecavir. The ANOVA model included the treatment received and the subject effect.

The test product could be considered as bioequivalent to the reference product, if the 90% confidence intervals for geometric least square mean ratios of Ln- transformed parameters Cmax and AUC_{0-72h} of entecavir fell within the acceptance range of 80.00 - 125.00 %.

Results

Table 2. Pharmacokinetic parameters for entecavir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	28.9253	5.49033	27.4476	5.54524
$AUC_{(0-\infty)}$	Not reported	Not reported	Not reported	Not reported
C_{max}	10.3315	2.38652	9.4386	1.77498
T_{max}*	0.67 (0.50 – 1.25)		0.84 (0.50 - 1.50)	

AUC0-72h area under the plasma concentration-time curve from time zero to 72 hours

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity

Cmax maximum plasma concentration

Tmax time for maximum concentration (* median, range)

Table 3. Statistical analysis for entecavir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Inter subject CV%*
$AUC_{(0-72h)}$	105.56%	96.90% - 114.98%	20.0
C_{max}	108.40%	98.61% - 119.16%	22.2

* estimated from the Residual Mean Squares

Safety data

As a part of safety monitoring during the study conduct, the subject vitals were performed at defined intervals as specified in the Ethics Committee approved protocol i.e., at 0.00, 1.0, 3.0, 12.0, 24.0 and 36.0 hours post-dose and adverse event monitoring (subject wellbeing questionnaire) was done at 1.0, 3.0, 12.0, 24.0 and 36.0 hours post-dose of each period.

No serious adverse events were reported in the study. One adverse event (headache) was reported for one subject during period I. The adverse event was considered mild in intensity and possibly related to the reference product.

Conclusions

Based on the presented bioequivalence study(318-13) Entecavir 1 mg Film-coated Tablets (Test) of Mylan Laboratories Limited, India is considered bioequivalent with Baraclude 1 mg Film-coated Tablets (Bristol-Myers Squibb Pharma EEIG).

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, a literature review of the non-clinical and clinical data for the active substance has been submitted, together with the results of a bioequivalence study conducted with the 1 mg strength. The biowaiver request for the 0.5 mg strength is considered acceptable.

The study was a single-dose, open-label, laboratory-blinded, two-treatment, randomized, balanced, single-period oral bioequivalence study, with a parallel design, conducted on healthy volunteers under fasting conditions. The parallel design of the study has been justified by the applicant throughout the procedure. The treatment groups can be considered comparable. Taking into account the comparability between groups and the expected terminal half-life of 128-149 hours for Entecavir, the parallel design is considered acceptable by CHMP.

Entecavir was determined in EDTA plasma using HPLC-MS/MS. The bioanalytical method was adequately described and validated. Long-term stability data of entecavir in K3EDTA plasma at -20 °C and -70 °C have been provided, and CHMP considered that presented results were reassuring.

2.4.6. Conclusions on clinical aspects

Based on the findings of the submitted bioequivalence study, Entecavir 1 mg Film-coated Tablets (Test) of Mylan Laboratories Limited, India and Baraclude® 1 mg Film-coated Tablets (Bristol-Myers Squibb Pharma EEIG) are considered bioequivalent with respect to rate and extent of absorption.

Biowaiver criteria are considered fulfilled and the bioequivalence conclusions can be extended to the 0.5 mg strength.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Exacerbation of hepatitis • Entecavir Resistance • Emergence of resistant HIV in HIV/HBV co-infected patients not

Summary of safety concerns	
	currently receiving effective HIV treatment
Important potential risks	• Carcinogenicity • Mitochondrial toxicity
Missing information	• Use in the paediatric population • Use in pregnancy • Use in elderly patients (≥65 years of age) • Use in severe acute exacerbation of chronic Hepatitis B • Long term safety and clinical outcomes data

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Exacerbation of hepatitis	• Sections 4.4 and 4.8 of the SPC contain adequate information on exacerbation of hepatitis • Sections 2,3 and 4 of the PL contain adequate wording in layman language • Product is POM only	None
Important identified risks: Entecavir resistance	• Sections 4.2, 4.4 and 5.1 of the SPC contain adequate information on entecavir	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	resistance. • Section 3 of the PL contains adequate wording in layman language • Product is POM only	
Important identified risks: Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment	• Sections 4.4 and 5.1 of the SPC contain adequate information on emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. • Section 2 of the PL contains adequate wording in layman language • Product is POM only	None
Important potential risks: Carcinogenicity	• Sections 5.3 of the SPC contain adequate information on carcinogenicity • Product is POM only	None
Important potential risks: Mitochondrial toxicity	• Sections 4.4 and 4.8 of the SPC contain adequate information on Mitochondrial toxicity (lactic acidosis and hepatic steatosis) • Section 2 of the PL contains adequate wording in layman language	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Product is POM only	
Missing information: Use in the paediatric population	• Sections 4.1, 4.2, 4.4 4.5, 4.8, 5.1 and 5.2 of the SPC contain adequate information on use in paediatric population • Sections 1, 2, 3 and 4 of the PL contains adequate wording in layman language • Product is POM only	None
Missing Information: Use in pregnancy	• Sections 4.6 and 5.3 of the SPC contain adequate information on use in pregnancy • Section 2 of the PL contains adequate wording in layman language • Product is POM only	None
Missing Information: Use in elderly patients (≥65 years of age)	• Sections 4.2, 5.1 and 5.2 of the SPC contain adequate information on use in elderly patients (≥65 years of age) • Section 2 of the PL contains adequate wording in layman language • Product is POM only	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in severe acute exacerbation of chronic Hepatitis B (CHB)	• There is no reference in the SPC or package leaflet about the risk of use in severe acute exacerbation of chronic Hepatitis B (CHB). • Product POM only	None
Long term safety and clinical outcomes data	• The effects of long term use and discontinuation criteria are described in sections 4.2, 4.4 and 5.1 of the SPC • Product is POM only	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to lay-out of proposed Entecavir Mylan PL, is the same as the style used in another approved user tested PL texts of Mylan. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of entecavir film-coated tablet. The reference product is Baraclude.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and was considered sufficient by CHMP. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient by CHMP.

The bioequivalence study is the pivotal study of this application, with an open-label, balanced, randomized, two-treatment, single-period, parallel, single dose design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The reason for selecting parallel study design was based on the entecavir long half-life (approx. 128-149 hours) and the low inter-subject variability. Descriptive statistics of demographics (age,

were considered adequate by CHMP. The analytical method was validated. Pharmacokinetic and statistical methods applied were also considered adequate.

The test formulation of entecavir met the protocol-defined criteria for bioequivalence when compared with Baraclude. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was shown.

CHMP concluded that the B/R balance for entecavir Mylan is positive.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Entecavir Mylan is favourable in the following indication:

> Entecavir Mylan is 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)

For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B, see sections 4.2, 4.4 and 5.1.

Entecavir Mylan 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. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, and 5.1.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.