18 May 2017
EMA/CHMP/294/877/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Isentress

International non-proprietary name: raltegravir

Procedure No. EMEA/H/C/000860/X/0059

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-12hr	Area under the curve from 0 to 12 hours post-dose
BID	Twice daily
BLOQ	Below the assay limit of quantitation
C12hr	Concentration at 12 hours post-dose
CPP	Critical process parameter
CQA	Critical Quality Attribute
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
EP	European Pharmacopoeia
EU	European Union
FCT	Film-coated tablet
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good clinical practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Loss on drying
LS means	Least-squares means
MA	Marketing Authorisation
MS	Mass Spectrometry
NC=F	Non-completer=failure
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
NRTI	Nucleoside reverse transcriptase inhibitor
OOS	Out of Specifications
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
QC	Quality Control
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TDF	Tenofovir disoproxil fumarate
Tmax	Time to Cmax
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

UV	Ultraviolet
VF	Virological failure
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Merck Sharp & Dohme Limited submitted on 27 May 2016 an extension of the marketing authorisation.

The MAH applied for a change or addition of a new strength of 600mg film coated tablets.

The MAH initially applied for the following indication for Isentress 600mg film coated tablets:

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV 1) infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

Furthermore, the PI is brought in line with the latest QRD template version 10.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(c) - Extensions of marketing authorisations

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 MAH 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 MAH received Scientific Advice from the CHMP on 29 July 2015, 21 September 2006 and 25 July 2008. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey

- The application was received by the EMA on 27 May 2016.
- The procedure started on 16 June 2016.
- The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on 3 September 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 13 September 2016.
- During the meeting on 29 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 13 October 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 10 March 2017.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at a sponsor site in the United States, between 9 January 2017 to 13 January 2017, and a GCP inspection at an investigator site in South Africa, between 12 December 2016 and 15 December 2016. The outcome of the inspections carried out was issued on 9 March 2017.
- The CHMP Rapporteur and PRAC Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on 24 April 2017, and updated versions on 11 May 2017, 12 May 2017 and 15 May 2017.
- During the PRAC meeting on 5 May 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The CHMP Rapporteur and PRAC Rapporteur circulated updated versions of the Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on 11 May 2017, 12 May 2017 and 15 May 2017, respectively.
- During the meeting on 18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Isentress.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

HIV is the virus that causes the Acquired Immune Deficiency Syndrome (AIDS). HIV infects and leads to a depletion of immune cells (CD4 + cells). As the CD4-positive cells are depleted, the host becomes increasingly susceptible to a variety of opportunistic pathogens and immune deficiency related diseases. In the absence of treatment, most infected individuals succumb to HIV-related disease.

2.1.2. Epidemiology

Since the beginning of the epidemic, more than 70 million people have been infected with HIV, of which about 35 million people have died. The epidemic has reached every country and nearly all populations throughout the world. The overall prevalence of HIV appears to have stabilized, or increased in some countries, likely due to increased survival of infected people because of antiretroviral treatment. However, the 2015 incidence of new HIV infections represents a decline of 38 percent from 2001, when there were 3.4 million new infections.

2.1.3. Biologic features

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress the HIV-1 viral load to levels that are at least below 50 copies/mL of blood.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Initial infection may cause nonspecific febrile illness. The risk of subsequent manifestations is related to immunodeficiency and is proportional to the level of CD4+ cell counts. Manifestations range from asymptomatic carriage to AIDS, which is defined by serious opportunistic infections or cancers or a CD4 count of < 200/µL. HIV infection can be diagnosed by antibody, nucleic acid (HIV RNA), or antigen (p24) testing. Screening should be routinely offered to all adults and adolescents. Treatment aims to suppress HIV replication by using combinations of 3 drugs that inhibit HIV enzymes; treatment can restore immune function in most patients if suppression of replication is sustained.

2.1.5. Management

Over 25 individual agents are licensed to treat HIV-1 infection. These agents are members of 6 distinct mechanistic classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors (EIs), integrase strand transfer inhibitors (InSTI; also commonly referred to as integrase inhibitors), and pharmacokinetic enhancers. Current guidelines for the management of treatment-naïve HIV-1 infected patients in various regions including the United States (US), United Kingdom (UK), and Europe (EACS) and elsewhere recommend 2 NRTIs and a third agent, generally of the InSTI or PI class.

HIV infection requires life-long therapy, and patients must be highly adherent to avoid virologic failure and the development of resistance. HIV-infected patients often have concomitant medical conditions, necessitating the use of multiple medications for non-HIV related conditions. Thus, any measure to simplify HIV treatment increases the potential for improved adherence and overall therapeutic success. Raltegravir, with a well-established safety and efficacy profile, is currently administered twice daily. Once daily administration of raltegravir, as a regimen of two 600 mg tablets, will simplify therapy and thus has the potential to increase effectiveness by enhancing adherence.

For HIV therapy, it is estimated that HIV patients must be at least 95% adherent to maintain long-term efficacy. A meta-analysis of 207 studies across multiple socioeconomic cohorts found that although adherence is strongly related to psychological factors and beliefs about the necessity of treatment, simpler

treatment regimens were also significantly related to adherence. Among factors affecting the complexity of a dose regimen, pill count, dosing frequency, and adverse experiences are among the most significant in affecting adherence

About the product

Raltegravir was the first approved InSTI ART. Raltegravir inhibits the HIV integrase enzyme from inserting viral DNA into the host genome, an essential step in HIV replication. Raltegravir 400 mg BID has demonstrated characteristics which make it a useful option as first-line therapy for HIV-infected patients. These characteristics include potent antiviral activity, a favourable tolerability and safety profile, and few and manageable drug-drug interactions (DDIs). A once daily raltegravir dosing option would provide a more convenient treatment option for HIV-1 infected treatment-naïve patients and for continued treatment in patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID, in adults and also in paediatric patients weighing at least 40 kg. It would facilitate adherence and improve the probability of achieving and maintaining optimal efficacy while retaining many of the favourable attributes of the ISENTRESS® 400 mg BID regimen.

Type of Application and aspects on development

- Legal basis

This application is made under Article 8(3) for an extension of an EU marketing authorisation via the centralised procedure for a known active substance Raltegravir.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing raltegravir potassium salt as active substance equivalent to 600 mg of raltegravir.

Other ingredients are:

For the tablet core: microcrystalline cellulose, hypromellose 2910, magnesium stearate, croscarmellose sodium.

For the film-coating: lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, black iron oxide.

The tablet may also contain trace amount of carnauba wax.

The product is available in HDPE bottle with a child-resistant polypropylene closure, induction seal and silica gel dessicant as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The active substance raltegravir potassium salt is identical to that used in the authorised products (Isentress 400 mg tablet, 25 and 100 mg chewable tablets and 100 mg /sachet granules for an oral suspension). However to improve tensile strength of the formulation the active substance used in the 600 mg film coated tablets is being jet milled which impacts the particle size distribution as well as the hygroscopicity. The milled active substance is slightly hygroscopic. The particle size of the milled raltegravir active substance has been characterised by laser diffraction technique. The particle size distribution of the milled raltegravir active substance is unimodal.

Raltegravir was characterised by X-Ray Powder Diffraction (XRPD) and shown to be a crystalline material. In addition to anhydrous Form C, the potassium salt of raltegravir has two other known crystalline anhydrous polymorphs denoted as Form A and Form B. The XRPD patterns for all crystalline forms are different and XRPD has been used to routinely differentiate the multiple crystalline forms. Solubility studies showed Form C to be the most thermodynamically stable phase under the commercial crystallisation process conditions. Additionally, from hygroscopicity experiments, Form C is not hygroscopic at 95% or lower relative humidities at 25°C, and no solid-state inter-conversion between anhydrous Form C and monohydrate has been observed under any relative humidity conditions at 25ºC. The potential for the milling operation to result in polymorphic form conversion of the active substance was evaluated using XRPD and Differential Scanning Calorimetry (DSC). The results for all tests are consistent with Anhydrous Form C, the desired form, indicating that polymorphic form conversion does not occur during the milling process.

For information on the unmilled active substance reference is made to Module 3.2.S of the marketing authorisation of the authorised Isentress products.

Manufacture, characterisation and process controls

The active substance is manufactured using third generation synthetic route as described in the approved registration of already authorised tablet. The active substance manufactured per the approved manufacturing process is then milled by passing the material through a jet-mill.

The active substance is packaged in double LDPE liners closed separately with twist ties inside a HDPE drum. The inner liner may be heat sealed. The milled active substance is stored under nitrogen in this container closure system. The LDPE liners comply with Ph. Eur. 3.1.3 and European Directive EU 10/2011 including modifications with 2015/174 .

Specification

The milled active substance specification includes tests for: characteristics, identity (potassium test, IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size (laser diffraction).

The specifications for the milled raltegravir active substance are identical to those listed in the currently approved tablets with the exception of the individual unspecified impurity and particle size distribution for which tighter limits are proposed for the active substance used in the new 600mg film coated tablet.

The analytical procedures with the exception of particle size distribution are the same as in the currently approved tablets. The analytical method used for particle size distribution has been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data on eight scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

A retest period of 36 months when stored below 30°C is approved for un-milled raltegravir active substance for the already approved tablets.

Stability data were provided for nine scale batches of milled active substance, from the proposed manufacturers, stored in the intended commercial package for up to 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested*:* characteristics, assay, impurities, water content, particle size. The analytical methods used were the same as for release and were stability indicating.

No significant changes were observed. All tested parameters were within the specifications.

The stability results indicate that the milled active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored below 30ºC in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The quantitative composition of the yellow, oval-shaped 600 mg film-coated tablet is provided.

The aim of this line extension is to introduce a 600 mg strength of raltegravir potassium salt film-coated tablets. The new strength was developed for once daily use (two 600 mg tablets taken one time daily) in order to reduce the pill burden and offer physicians and patients a more convenient raltegravir regime. The pharmaceutical development of the finished product contains QbD elements. Its objective was to develop a solid oral dosage form that meets safety and efficacy requirements of the Quality Target Product Profile (QTPP) throughout the shelf life of the product. Relevant aspects of the QTPP that influenced commercial product development are listed in Table 1.

Table 1. Finished product Quality Target Product Profile (QTPP)

Clinical Attributes	
Indication/Mechanism	HIV (Integrase inhibitor)
Treatment	Chronic
Route of Administration	Oral
Dose/Dose Frequency	2x 600 mg Raltegravir / QD

Safety and Efficacy	
Impurities and Degradation Products	Controlled below ICH Q3 or qualified levels that do not impact product performance
Patient adherence Requirements	
Subjective Properties	Two film coated tablets, with smaller image than 1.6 g for QD dosing
Food Effect Consideration	No food restrictions
Shelf Life	At least 2 years

The critical quality attributes (CQAs) identified were: appearance, degradation products, assay, dissolution, dose uniformity and water activity.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the film-coating material Opadry II yellow which is tested according to an in-house specification. In addition, the yellow iron oxide (E172) and black iron oxide (E172) used in Opadry II yellow excipient are in compliance with current EU Directives concerning the use of colouring agents. 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. The role, the choice of the excipients and their concentration has been satisfactorily justified. The additional controls on the degree of acid carboxymethyl substitution for croscarmellose sodium and particle size for the microcrystalline cellulose have been justified.

The finished product is also for paediatric use, for paediatric patients weighing at least 40 kg. The tablets are yellow, oval-shaped, with the following dimensions 19.1 mm x 9.7 mm x 6.1 mm. The tablets are considered age appropriate.

During pharmaceutical development three different formulations were developed: one for Phase 1, one for Phase 3 clinical trials and the formulation proposed for commercial use. The phase 1 and phase 3 tablets differed only in minor change to the non-functional film-coat composition (addition of colorant). The tablets used in phase 3 and the formulation proposed for commercial use had different OPADRY II non-functional film-coatings and were demonstrated to be similar in comparative dissolution studies. The Phase 1 and Phase 3 tablet formulations had the same core tablet composition as the intended commercial product.

A fluid bed granulation process was initially developed and utilised to establish the granulation composition. Fluid bed granulation was initially preferred over high shear wet granulation (HSWG) due to the perceived risk of raltegravir hydrolysis. After further evaluation and establishment of raltegravir stability in a wet system, high shear wet granulation was explored and developed as the commercial process for its favourability to produce denser granulation.

Raltegravir 600 mg active product has been developed through a systematic risk-based development program to achieve a robust manufacturing process. The development of the intended commercial manufacturing process and the studies conducted across a variety of scales is described in detail. The objective was to develop a robust process to ensure the finished product consistently meets the critical quality attributes (CQA).

A risk assessment of the major unit operations, high shear wet granulation, blending, lubrication, compression, and film coating was performed. The assessment identified areas of risks that needed to be addressed during development. Subsequent process development was focused on the risks that had the highest potential to impact the CQAs of the finished product.

The use of prior knowledge from Isentress 400 mg tablets was limited because the raltegravir granules for this product are manufactured using high shear wet granulation vs. roller compaction for Isentress 400 mg tablets.

Process parameter ranges were developed at small and pilot scale and studied again and verified at the intended commercial manufacturing site.

A control strategy has been established at the commercial site to ensure that the process parameters remain within the defined process parameter ranges (Proven Acceptable Ranges (PARs)) for commercial production.

Satisfactory information has been presented on the development of the dissolution test and the test conditions have been justified. While the proposed dissolution test has been demonstrated to be sensitive to manufacturing parameters for granulation level, compression force, and granulation wet- hold time, the Applicant has acknowledged that the limits as proposed fail to discriminate between batches with differences in these manufacturing variables as all batches will pass the dissolution criteria. The figures presented showed that that the dissolution profiles obtained for the batches with differences in granulation level, compression force, and wet-hold time are consistent with the range of dissolution performance obtained for batches used in clinical studies.

However, batches expected to be outside of clinical experience (e.g., open dish storage at 40°C/75% RH) do fail the proposed dissolution criteria. Comparative data for the 400 mg and 600 mg formulations using the proposed commercial dissolution method for raltegravir 600 mg tablets have been presented and results showed that the profiles can be distinguished. The dissolution method is considered acceptable.

The primary packaging is a HDPE bottle with a child-resistant polypropylene closure, induction seal and silica gel desiccant. The bottle materials comply with Ph.Eur. and EC requirements. The Applicant confirmed the child resistant container/closure complies with the International Standard (EN ISO 8317) Child-resistant packaging – Requirements and testing procedures for re- closable packages. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of eight main steps: granulation, wet milling, drying, milling, blending and lubrication, compression, film coating, packaging. The process is considered to be a standard manufacturing process.

The description of the manufacturing process includes the Normal Operating Ranges (NOR) and target values for each of the process parameters in addition to the Proven Acceptable Ranges (PARs). Assurance has been provided, as requested, that only one parameter at a time will be varied from the target set points.

The drying step and the compression step were identified as critical steps. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Adequate justification for holding times of intermediates (granulated material, bulk film coated tablet) has been provided. Justification has been provided to justify not defining the wet hold time as a Critical Process Parameter (CPP). The justification is considered acceptable.

Process validation will be performed post authorisation and a suitable Process Validation Scheme has been provided.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: description, identity (HPLC, UV, NIR as an alternative method to UV method), assay (HPLC), degradation products (HPLC), uniformity of dosage units –weight variation (Ph. Eur.), dissolution (HPLC), microbial limits (Ph. Eur.).

The water activity level of the tablets is controlled by manufacturing process conditions, controlled relative humidity in the manufacturing and packaging areas, and the product package. These controls consistently resulted in batches with water activity ≤ 0.35. The water activity values then only decreased slightly through the 9 months formal stability studies as the desiccant in the bottle ensures water activity remains below critical levels throughout shelf life. As a result of the various controls, the water activity for the finished product was confirmed to be less than critical levels for microbial growth, dissolution slowdown, and raltegravir potassium salt disproportionation. Therefore, water activity was accepted not to be included as a release or shelf-life test. A finished product test for moisture was also accepted not to be included in the specification as moisture levels are controlled by the maintenance of low water activity levels. The moisture values have not changed significantly through the 9 month time point of the formal stability studies.

A small and consistent disproportionation of raltegravir potassium to raltegravir free phenol is observed in the finished product. This occurs between the croscarmellose sodium (CCNa) and raltegravir salt dissolved in the granulating fluid in the high shear granulation process (maximum predicted free phenol is 2.9%). Additional disproportionation may occur in the tablet between raltegravir and the extragranular CCNa, but only at humidity levels (>45% RH) which allow sufficient water adsorption to facilitate the reaction. To control the formation of free phenol in this product, the degree of acid carboxymethyl substitution in croscarmellose sodium is limited and the water activity of the finished product is controlled during manufacturing, packaging and storage. Based on the controls implemented and stability results, a finished product test for raltegravir free phenol is not proposed.

A finished product test for hardness is not proposed. Hardness within the proven acceptable range has not been shown to significantly impact the dissolution of the product. Also, no significant change in hardness has been observed in stability. The in-process hardness controls proposed are considered adequate to ensure quality of the product.

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 assay and impurities testing has been presented.

Batch analysis results are provided for six pilot scale batches manufactured at the proposed commercial site using both registered active ingredient sources confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch analysis results are provided for batches from other manufacturing sites.

Stability of the product

Stability data were provided for six pilot scale batches of finished product manufactured at the proposed commercial site using both active ingredient sources. The batches were stored under long term conditions for 18 months at 25 ºC / 60% RH, under intermediate conditions for 18 months at 30 ºC / 75% RH and for six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging representative of those proposed for marketing. Samples were tested for appearance, assay, degradation

products and dissolution. In addition to the specification test methods, moisture content, water activity, hardness, free phenol content and microbial quality were evaluated during the formal stability studies. The analytical procedures used are stability indicating.

No significant changes in appearance, assay, degradation products, dissolution, moisture, hardness and free phenol content were observed at any time point or storage condition. There was a decrease in water activity through the study. However, the change in water activity had no impact on any of the other quality characteristics of the finished product.

In addition, three batches were exposed to light in accordance with the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results showed that the proposed 600mg tablet is stable when exposed to light.

An in-use stability study was carried out by simulating a patient's in-use practice in the 60 count HDPE bottles at 30 ºC/75%RH for up to 8 weeks. Results support the proposed in-use stability shelf life as mentioned in the SmPC.

Based on available stability data, the proposed shelf-life of 24 months with the following storage statement “Keep the bottle tightly closed, with the desiccant in order to protect from moisture.” as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose 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.

It is also confirmed that magnesium stearate is derived from purely vegetable origin.

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. The applicant has applied QbD principles in the development of the finished product manufacturing process. However, no design space was claimed. 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. Recommendations for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

The MAH did not provide any additional non-clinical data as no new non-clinical studies for raltegravir in support of this application were conducted. The raltegravir 1200 mg Once Daily (QD) development program and application are fully supported by non-clinical studies previously conducted in support of the raltegravir 400 mg twice daily (BID) regimen (ISENTRESS).

Raltegravir for once daily use (a 1200 mg dose consisting of two 600 mg tablets) allows for a simplified dosing regimen that will provide a convenient backbone for antiretroviral therapy regimens and will allow flexibility in the choice of other additional once daily agents that could improve patient compliance and satisfaction.

2.3.2. Pharmacology

No new non-clinical pharmacodynamic studies have been conducted to support the raltegravir 1200 mg QD development program. Findings from in vitro studies previously conducted in support of raltegravir 400 mg BID regimen pertain to raltegravir 1200 mg QD as they are independent of the formulation or frequency of its administration. These studies included: comprehensive evaluation of its in vitro biochemical and antiviral activities including its resistance profile, its activity against other enzymes and receptors, and its antiviral activity in combination with other antiretroviral agents. The safety pharmacology studies previously conducted in support of the raltegravir 400 mg BID application demonstrated that raltegravir evoked no significant ancillary pharmacological or behavioural effects when evaluated on a diverse range of physiological functions (cardiovascular, neurobehavior, respiratory) in vivo.

2.3.3. Pharmacokinetics

No new non-clinical pharmacokinetic studies have been conducted to support the raltegravir 1200 mg QD development program. The non-clinical pharmacokinetic studies previously conducted in support of raltegravir 400 mg BID regimen included: comprehensive evaluation of absorption, distribution, metabolism, and excretion (ADME) of raltegravir in rats and dogs (two species selected for the toxicological evaluation of the compound); the metabolism in CD-1 mice, the second species in which the carcinogenic potential of raltegravir was studied; evaluation of raltegravir as a substrate, inhibitor and inducer of major cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGT) enzymes. For the purpose of interspecies comparisons between non-clinical animal models and humans, protein binding, metabolism, and excretion of raltegravir in humans were also discussed. In addition, the assessment of the inhibitory effect of raltegravir on major human drug uptake and efflux transporters was presented in the publication by the Applicant [Ref. 4.3: 03Z7Q3]. The findings from the above studies conducted in support of raltegravir 400 mg BID regimen, including the in vitro assessment of raltegravir drug-drug interaction (DDI) potential, are applicable to raltegravir 1200 mg QD.

Raltegravir is not a substrate of CYP enzymes and therefore, it is not expected to be a victim of DDIs via CYP inhibition or induction. Raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway and therefore, co-administration of potent UGT1A1 inhibitors or inducers may alter plasma levels of raltegravir. In vitro, raltegravir does not inhibit (IC50>100 µM) CYP1A2, CYP2B6, CYP2C8,

CYP2C9, CYP2C19, CYP2D6 and CYP3A, or induce CYP1A2, CYP2B6 and CYP3A4. In addition, raltegravir is not a potent inhibitor (IC50>50 μM) of the UGTs tested (UGT1A1, UGT2B7) or the major human drug efflux and uptake transporters in vitro. Raltegravir does not inhibit P-glycoprotein and inhibits only 22% of breast cancer resistance protein (BCRP)-mediated transport at 100 μM. Raltegravir does not inhibit organic anion transporting polypeptide (OATP) 1B1, and it shows 40% inhibition of OATP1B3 and 16% inhibition of organic cation transporter (OCT)1 at 100 μM in vitro. In vitro, raltegravir also does not inhibit OCT2 and is not a potent inhibitor of organic anion transporter (OAT)1 and OAT3 (IC50 of 108 μM and 18.8 μM, respectively), and multidrug and toxin extrusion proteins (MATE)1 and MATE2-K (52% and 29% inhibition at 100 μM, respectively).

Based on in vitro data, raltegravir has overall, a low propensity to perpetrate clinically meaningful DDIs with substrates of major drug metabolizing enzymes or drug transporters at plasma concentrations following 1200 mg QD administration (median C_{max} of 16.8 μM; calculated unbound Cmax of 2.8 μM). The potential for raltegravir to inhibit the renal uptake transporter OAT3 at maximal concentrations following 1200 mg QD cannot be completely excluded based on in vitro data, however clinically meaningful DDI via this mechanism is unlikely.

2.3.4. Toxicology

No new non-clinical toxicity studies have been conducted to support the raltegravir 1200 mg QD development program. The non-clinical toxicity studies previously conducted in support of raltegravir 400 mg BID regimen support clinical administration of raltegravir 1200 mg QD. All excipients in the raltegravir 1200 mg QD tablet are commonly used in pharmaceutical manufacturing, and no new impurities or degradation products were identified in the drug product.

The previously conducted non-clinical toxicity evaluation demonstrated that raltegravir is generally well-tolerated. Maximum oral and intravenous doses based on tolerability, formulation feasibility and/or plateau of exposure were used in toxicity studies to define the toxicity profile of raltegravir, with safety margins for the 1200 mg raltegravir dose determined for each of the toxicities identified. Effects in rodents (mortality, body weight loss, and non-glandular stomach irritation) were attributed to the non-clinical raltegravir formulation's well-characterized bulk dosing volume and local irritant effect following oral gavage of the non-clinical formulation and are not considered of significant risk to humans. There were no adverse effects in dogs up to the highest doses tested (plateau in systemic exposure).

In developmental and reproductive toxicity studies, raltegravir has been shown not to pose a hazard to reproduction or to the developing foetus based on studies in rats and rabbits. In developmental toxicity studies in rats, a slight increase in the incidence of supernum erary ribs relative to control was found at the top dose of 600 mg/kg/day. There were no external or visceral abnormalities and no other fetal or postnatal developmental effects at this dose. The safety margin at the NOEL for developmental toxicity in rats is approximately 3.5-fold relative to the expected human AUC in patients administered therapeutic doses of raltegravir (either raltegravir 1200 mg QD or raltegravir 400 mg BID); in rabbits, no developmental toxicity was found at the maximum dose of 1000 mg/kg/day, resulting in a safety margin of about 3.7-fold relative to the expected maximal human AUC at the therapeutic dose. In a toxicokinetic study in pregnant and lactating rats, raltegravir was shown to cross the placental barrier with foetal exposure values up to 1.5- to 2.5-fold greater than in maternal plasma drug concentrations and was also present in rat milk at concentrations about 3-fold compared to plasma. There were no effects on male or female fertility, on prenatal and postnatal development or on juvenile development in rats orally administered raltegravir.

Raltegravir was not genotoxic in a battery of in vitro assays in bacteria and mammalian cells designed to detect mutagenicity, direct DNA damage, or clastogenicity. Raltegravir was not shown to be a direct carcinogen when administered to rats and mice for 2 years. Localization of raltegravir to the nose/nasopharynx was determined to occur from routine techniques of oral gavage with periodic aspiration of dosing material into the nose and nasopharynx , resulting in secondary neoplastic findings attributed to chronic irritation and inflammation present within the nasopharynx and nose. The irritation potential of raltegravir was previously demonstrated in shorter duration rodent studies and in local tolerance studies.

Based on the proposed mechanism, the observed neoplasia of the nose and nasopharynx of rats is considered to have minimal relevance to humans.

2.3.5. Ecotoxicity/environmental risk assessment

Using all default values for market penetration and no removal in the environment, the Predicted Environmental Concentration (PEC) based on maximum daily dose for currently marketed productsis determined to be 8 µg/L. The maximum daily dose of raltegravir associated with this application is 1200 mg/day which corresponds to a PEC of 6 µg/L. Therefore, predicted environmental concentrations are anticipated to be equal to or lower than those already approved. No significant increase in the environment is expected to occur as a result of this application.

2.3.6. Conclusion on non-clinical aspects

No new non-clinical studies have been performed in support of this application. The data provided are considered to be sufficient to support the proposed use of raltegravir once daily.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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.

Table 2. Tabular overview of clinical studies

Study number	Study Treatment	Number of Subjects Receiving Raltegravir†	Key Purpose
290	Raltegravir 1200 mg (2 x 600 mg tablets) Raltegravir 1200 mg (3 x 400 mg tablets)	36 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	Food Effect
291	Raltegravir 1200 mg QD (2 x 600 mg tablets) for 5 days Raltegravir 1200 mg QD (3 x 400 mg tablets) for 5 days Raltegravir 400 mg BID (1 x 400 mg tablet) for	24 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	PK

	5 days		
293	Raltegravir 1800 mg QD (3 x 600 mg tablets) for 28 days	24 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	PK and safety
812	Raltegravir 1200 mg QD (2 x 600 mg tablets); Efavirenz 600 mg QD (1 x 600 mg tablet) + raltegravir 1200 mg QD (2 x 600 mg tablets) on Day 12	21 Healthy male and female subjects ≥ 19 and ≤ 55 years of age	Drug- Drug Interaction
823	Raltegravir 1200 mg QD (2 x 600 mg tablets); Atazanavir 400 mg QD (2 x 200 mg tablets) + raltegravir 1200 mg QD (2 x 600 mg tablets) on Day 7	14 Healthy male and female subjects ≥ 19 and ≤ 55 years of age	Drug- Drug Interaction
824	Raltegravir 1200 mg QD (2 x 600 mg tablets) 5 days prior to Period 1; Raltegravir 1200 mg QD (2 x 600 mg tablets) Raltegravir 1200 mg QD (2 x 600 mg tablets) + 3 tablets of TUMS® Ultra Strength (US) 1000 mg given concomitantly Raltegravir 1200 mg QD (2 x 600 mg tablets) + 20 mL MAALOX® Maximum Strength (MS) given 12 hours After administration Raltegravir 1200 mg QD (2 x 600 mg tablets) + 3 tablets of TUMS® Ultra Strength (US) 1000 mg given 12 hours after administration	22 HIV-infected volunteers Male and female subjects ≥ 19 and ≤ 55 years of age	Drug- Drug Interaction
292	Raltegravir 1200 mg QD (2 x 600 mg tablets) + TRUVADA™ QD; Raltegravir 400 mg BID (1 x 400 mg tablet) + TRUVADA™ QD	802 Male and female HIV-1 infected, treatment-naïve subjects ≥ 18 years of age	Interventional

2.4.2. Pharmacokinetics

Raltegravir 1200mg (QD) given once a day as 2X600mg tablets is absorbed with a median T max of approximately 1.5 to 2 hours in the fasted state.

Bioavailability

When compared to both raltegravir 400 mg BID (2 x 400 mg tablets) and raltegravir 1200 mg QD (3 x 400 mg tablets), raltegravir 1200 mg QD (2 x 600 mg tablets) has a higher systemic exposure.

In Study P291, an open-label, multiple-dose, randomized, three-period, three-treatment, six-sequence, crossover, comparative bioavailability study designed to assess the pharmacokinetics of raltegravir after a multiple dose administration for five days of reformulated Raltegravir 600 mg Tablets (1200 mg QD) (Treatment A) and Isentress® 400 mg Tablets (1200 mg QD (Treatment B) and 400 mg q12 (Treatment C)) in which the pharmacokinetic (PK) parameters AUC_{24}, C_{max}, C_{trough} (C24) and T_{max} for Treatments A and B and AUC_{12}, C_{max}, C_{trough} (C12), Tmax and AUC_{24} (AUC12 x 2) for Treatment C were estimated using a non-compartmental approach.

Administration of the 1200 mg dose given as 2 x 600 mg tablets once daily resulted in a GM (CV%) C_{trough} of 81.1nM (72%), AUC_{0-24} of 59.5µM-hr (34%) and C_{max} of 20.6µM (44%) on Day 5

Administration of the 1200 mg dose given as 3 x 400 mg tablets once daily resulted in a GM (CV%) C_{trough} of 83.5nM (53%), AUC_{0-24hr} of 49.0 µM-hr (73%), and Cmax of 14.1µM (99%) on Day 5

Administration of the 400 mg dose given twice daily resulted in a GM (CV%) C_{trough} of 130.9 nM (56%), AUC_{0-24} (2 x AUC_{0-12}) of 25.4 µM-hr (106%), and C_{max} of 3.4 µM (153%) on Day 5

Influence of food

Study P290 was conducted to the effect of a low-fat and a high-fat breakfast on the pharmacokinetics (Cmax, AUC_{inf} and C_{24}) of raltegravir 1200 mg dose (2x600mg) and Isentress® 400 mg Tablets (3 x 400 mg). Administration of a 1200 mg dose as 2 x 600 mg tablets in the fasted state resulted in a geometric mean (GM) C24hr of 57.7 nM, Cmax of 22.6 µM, and AUC0-last of 56.5 µM-hr. Administration of a low-fat meal resulted in a 42% decrease in AUC0-last, 52% decrease in C_{max}, and 16% decrease in C24hr. Administration of a high-fat meal resulted in a 1.9% increase in AUC0-last, 28% decrease in C_{max}, and 12% decrease in C24hr.

Administration of a 1200 mg dose as 3 x 400 mg tablets in the fasted state resulted in a GM C24hr of 46.7 nM, Cmax of 9.2 µM and AUC0-last of 33.8 µM-hr. Administration of a low-fat meal resulted in a 73% decrease in AUC0-last, 75% decrease in Cmax, and 18% decrease in C24hr. Administration of a high-fat meal resulted in a 39% increase in AUC0-last, 23% decrease in Cmax, and 70% increase in C24hr.

Distribution

Raltegravir is moderately bound (83%) to proteins in human plasma in vitro. Raltegravir does not significantly partition into human blood cells in vitro, with a blood-to-plasma concentration ratio of 0.6. In vitro studies show that raltegravir is a P-glycoprotein (P-gp) substrate.

Elimination

The major elimination pathway of raltegravir is via UGT 1A1-mediated glucuronidation. Similar to the raltegravir 400 mg BID formulation, the apparent terminal elimination half-life of the 600 mg tablet formulation is approximately 9 to 12 hours with a shorter α-phase half-life (~1 hour) accounting for much of the AUC.

Special populations

Impaired renal function

No renal impairment study was performed with the proposed raltegravir 1200 mg QD (as 2 x 600 mg tablets). Based on the renal impairment results described in previous raltegravir submissions, no specific clinical recommendation is needed for raltegravir 1200 mg QD (2 x 600 mg) dosing.

Impaired hepatic function

No hepatic impairment study was performed with the proposed raltegravir 1200 mg QD (as 2 x 600 mg tablets). Based on the hepatic impairment results described in previous raltegravir submissions, no specific clinical recommendation is needed for raltegravir 1200 mg QD (2 x 600 mg) dosing.

Children

Population PK modelling was conducted to define a weight cut-off that will support the use of 1200 mg QD (2 x 600 mg) in paediatric patients to find a weight range such that raltegravir exposures were contained within the exposure range determined to be safe in adults from PN292. The Pop PK model was based on data from the five Phase 1 studies (PN290, PN291, PN812, PN823, and PN824) and the Phase 3 study (PN292) in adults.

A fixed allometric scaling approach was used to simulate steady state exposures in HIV-infected paediatric patients following administration of raltegravir 1200 mg QD.

Results of the paediatric simulations showed that among the various subgroups evaluated, weight cut-offs range between 30 to 45 kg when comparing AUC0-24hr,ss in adult and paediatric patients. The highest cut-offs are identified in Black/other paediatric patients receiving TRUVADA both under fasted or high fat meal conditions; in these two groups the immediately lower weight group (≥ 40 and <45 kg) shows exposures that are just above the safety threshold but the difference appears to be negligible.

Pharmacokinetic interaction studies

Based on in vitro data, raltegravir is not a substrate of CYP enzymes and therefore, it is not expected to be a victim of DDIs via CYP inhibition or induction. Based on in vivo and in vitro studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway and co-administration of UGT1A1 inhibitors or inducers may alter plasma levels of raltegravir.

The applicant considers that the DDI studies conducted for Isentress can be extended to raltegravir 1200 mg QD but notes that that the criteria for a clinically important change in raltegravir PK are different for 1200 mg QD in comparison to 400 mg BID.

The applicant considers that no clinically relevant difference in the efficacy of raltegravir 1200 mg QD is anticipated for factors that decrease raltegravir C_{trough} by <25%; specifically, the lower bound of the 90% confidence interval (CI) of C_{trough} geometric mean ratio (GMR) must be >0.75. Additionally, no clinically relevant difference in the safety of raltegravir 1200 mg QD is anticipated for factors that increase raltegravir AUC0-24 by <100%; specifically, the upper bound of the 90% CI of AUC0-24 GMR must be <2.00.

In an open-label randomized, 2-period, fixed-sequence study to evaluate the effect of co-administration of efavirenz and (MK-0518) raltegravir on the plasma pharmacokinetic (PK) profile of raltegravir (study PN812), Raltegravir was rapidly absorbed with an observed median Tmax of 1.5 hours following both treatments. The geometric mean apparent terminal t½ values were similar following raltegravir alone and raltegravir + efavirenz (8.95 hours and 8.87 hours, respectively). Co-administration with efavirenz yielded GMRs (raltegravir + efavirenz/ raltegravir alone) (90% CIs) for raltegravir AUC0-∞, Cmax, and C24 of 0.86 (0.73, 1.01), 0.91 (0.70, 1.17), and 0.94 (0.76, 1.17), respectively.

In another open-label 2-period, fixed-sequence study under fed conditions to evaluate the effect of co-administration of atazanavir and raltegravir on the plasma pharmacokinetic (PK) profile of raltegravir (PN 823), Co-administration with atazanavir yielded GMRs (90% CIs) for raltegravir AUC0-∞, Cmax, and C24 of 1.67 (1.34, 2.10), 1.16 (1.01, 1.33), and 1.26 (1.08, 1.46), respectively. Since the upper 90% CI of the raltegravir AUC0-∞ GMR obtained in the presence of atazanavir exceeded the upper clinical bound (2.00), therefore co-administration of atazanavir with raltegravir QD is not recommended.

In study PN824 A non-randomized, single-site, open-label, 4-period, fixed sequence trial of 1200 mg raltegravir, alone or in combination with metal cation-containing antacids (TUMS® Ultra Strength (US, calcium carbonate) or MAALOX Maximum Strength (MS, magnesium/aluminum hydroxide) (or generic equivalent) in HIV-infected male and female subjects 18 years of age or older; Steady state Cmax, AUC0-24 and C24 of raltegravir decreased by approximately 74%, 72% and 48%, respectively when 1200 mg QD raltegravir is given concomitantly with 3 tablets of TUMS® Ultra Strength 1000. Median Tmax remained unchanged after Three (3) tablets of TUMS Ultra Strength 1000 and 1200 mg QD raltegravir given concomitantly relative to 1200 mg QD raltegravir alone.

Steady state Cmax, AUC0-24 and C24 of raltegravir decreased by approximately 14%, 14% and 58%, respectively, when 20 mL MAALOX MS (or generic equivalent) is given 12 hours after administration of 1200 mg QD raltegravir. Median Tmax remained unchanged after Twenty (20) mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg QD raltegravir relative to 1200 mg QD raltegravir alone.

Steady state Cmax, AUC0-24 and C24 of raltegravir decreased by approximately 2%, 10% and 57%, respectively, when 3 tablets of TUMS® Ultra Strength 1000 is given 12 hours after administration of 1200 mg QD raltegravir. Median Tmax remained unchanged Three (3) tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg QD MK-0518 relative to 1200 mg QD raltegravir alone.

Exposure relevant for safety evaluation

Exploratory safety analyses based on raltegravir exposure quartiles were conducted using steady state AUC0-24 and Cmax for each subject in PN292 that were determined using the population PK model described in section 2.1.9.

There was no significant difference was observed in the reports of clinical and laboratory adverse events in study PN292 for subjects in the highest quartile of raltegravir exposure (69 µM*hr to 365 µM *hr for AUC0-24 and 20.5 µM to 48 µM for Cmax) when compared to subjects in the lower quartiles (16.5 to 69 µM*hr for AUC0-24 and 1.8 to 20.5 µM for Cmax). There was no trend observed related to increasing raltegravir exposure across the quartiles.

2.4.3. Pharmacodynamics

In previous applications, Ctrough (i.e. C24hr for raltegravir has been noted to be the appropriate PK parameter for determining efficacy i.e. in study PN071, A Ctrough of 45 nM was considered to be the cut-off below which a greater risk of treatment failure was observed which corresponded closely to the 25th percentile of the distribution of Ctrough values (43.28 nM) for raltegravir 800 mg QD. For raltegravir 1200 mg QD, the 25th percentile value was 62.74 nM and therefore above the cut-off for which there is a higher risk of treatment failure.

Exposure-efficacy analysis was conducted to assess the relationship between PK and efficacy endpoints of raltegravir 1200 mg QD (2 x 600 mg) and ISENTRESS 400 mg BID using information from study PN292 in order to confirm its consistency with ISENTRESS® 400 mg BID PK/PD relationship. PK and week 48 efficacy data from the study were used which included 797 treatment naïve HIV patients; raltegravir 1200 mg QD (N=531) and ISENTRESS® 400 mg BID (N=266). PK endpoints were determined using observed sparse concentrations from both treatment groups. The following were included in the analyses;

- the geometric mean of all observed concentrations for individuals subjects (Call_obs)
- the geometric mean of the observed concentration between 22 and 26 hours post-dose for 1200 mg QD (C24_obs)
- the geometric mean of the observed concentration between 11 and 13 hours post-dose for 400 mg BID (C12_obs)

The population PK model developed for raltegravir 1200 mg QD was used to predict the steady-state Ctrough values at 24 hour post-dose (C24) in subjects from the QD treatment arm.

Efficacy endpoints included the primary and secondary endpoints from PN292 i.e. achieving HIV-1 RNA <40 copies/mL and change from baseline in CD4 cell count, respectively.

Logistic regression was conducted to examine the relationship between PK and HIV RNA <40 copies/mL, with screening viral load (≤ 100,000 or >100,000 copies/mL), baseline CD4 cell count, and hepatitis B and/or C co-infection included for covariate evaluation. Additionally, the percent of patients achieving the viral suppression target (HIV-1 RNA <40 copies/mL) was also evaluated by quartiles of the PK endpoints. For the change from baseline in CD4 cell count, Pearson's correlation and Spearman's rank correlation with PK were calculated.

The odds ratios of PK and log-transformed PK parameters showed no statistical evidence of an association between any of the raltegravir exposure endpoints and probability of achieving HIV-1 RNA <40 copies/mL.

In terms of the percent of patients achieving HIV-1 RNA <40 copies/mL there no suggestion of a trend or apparent relationship between viral suppression and the range of raltegravir exposures achieved from both treatment regimens in PN292. It would appear that a similar degree of viral suppression is achieved across all quartiles of the Ctrough values from raltegravir 1200 mg QD, including the lowest quartile (< 25th percentile) when compared with ISENTRESS 400 mg BID.

For the analysis of change from baseline in CD4 cell count (secondary Phase 3 efficacy endpoint), no significant correlation was found for the majority of the PK endpoints from both raltegravir treatment regimens in PN292. In patients with screening HIV-1 RNA ≤ 100,000 copies/mL and hepatitis B and/or C co-infection, a trend (p-value <0.05) was observed between change from baseline in CD4 cell count and Call_obs (Spearman' s rank correlation = 0.645 and 0.497) for both raltegravir treatment regimens, and combined Ctrough values (Spearman's rank correlation = 0.692) from both treatment regimens. However, due to the small sample size in these subgroups (N=11-13). The applicant considers that no clinically meaningful correlations were found between raltegravir PK endpoints and change from baseline in CD4 cell counts.

2.4.4. Discussion on clinical pharmacology

In order to characterise the pharmacokinetics of raltegravir 1200 mg QD, the applicant relies on BA/BE studies (PN290 and PN291) conducted to compare the PK of this new proposed posology with that of Isentress 400mg b.i.d. This approach is considered acceptable. The results of the studies suggest that raltegravir 1200 mg QD (2 x 600 mg tablets) has a higher systemic exposure and Cmax when compared to raltegravir 400mg b.i.d. however, the C_{trough} for raltegravir 1200 mg QD is lower than the 400mg b.i.d. regimen but the mean C_{trough} observed in study 291 is higher than the threshold of 45 nM associated with reduced efficacy in previous studies.

PKPD modelling focusses on the overall exposure (AUC), however the importance of C_{trough} is recognised, particularly in terms of defining a weight cut off for dosing children.

The effect of other drugs on the elimination of raltegravir is well characterised and strong inducers and inhibitors of UGT1A1 are not recommended. However further in vitro work, and a better discussion, is required to fully understand the potential for raltegravir to interact on other drugs.

For the enzymes: 2B6, 2D6 and UGT2B7 and transporters: OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE-1 and MATE-2k, further in vitro data at higher substrate concentrations to determine a Ki is required to rule out the possibility of DDIs. Alternatively a mechanistic static model may be used to provide further support for a lack of interactions. Dependent on the results of these investigations, the maraviroc and tenofovir interactions should be reconsidered in mechanistic terms. The MAH committed to submit the results once completed.

PK/PD viral dynamics modelling

A PK/PD viral dynamics model was developed linking drug concentrations to viral inhibition thereby to treatment outcome in order to characterize the exposure-response relationship for raltegravir efficacy and the implications of changes to the PK profile. The PK/PD viral dynamics model incorporates information about the entire concentration time profile of raltegravir. Using an E_{max} model incorporating an in vivo EC50, the raltegravir concentration versus time profile is converted to a profile of percent viral inhibition versus time with a calculated average inhibition over the dosing interval. From this average inhibition, again using the Emax model, a concentration can be calculated which would result in this same level of average inhibition over the dosing interval as if the concentration were held constant over the interval. This concentration is the Equivalent Constant Concentration, or ECC, and is the PK parameter which is used as the input in the viral dynamics model.

The in vivo EC50 values (raltegravir concentration resulting in 50% inhibition) for infectivity and cell activation were 3.5 ng/ml and 30 ng/ml, respectively, with simulation results being primarily driven by changes to the EC50 value associated with inhibition of infectivity. Raltegravir pharmacokinetic data from the Phase 1 study PN291 were used to assess the probability that the raltegravir pharmacokinetic profiles associated with 1200 mg QD raltegravir would result in efficacy similar to that obtained in adults with the recommended dose of 400 mg BID ISENTRESS. The full PK profiles obtained in PN291 were used to calculate a distribution of steady state ECC values for each treatment

The PK profiles for both formulations of raltegravir at a dose of 1200 mg QD are projected to result in virologic efficacy similar to that observed in adults taking the 400 mg BID dose. The PK/PD viral dynamics model suggested that 1200 mg QD reformulated raltegravir has a high probability of demonstrating non-inferiority to 400 mg BID

The PKPD modelling appears to show that responses are at the top of the concentration response curve and therefore changes in exposure do not have a big impact on efficacy.

The viral dynamic model allows a more mechanistic understanding of the PKPD and change in profile shape versus efficacy and thus is considered to be useful.

2.4.5. Conclusions on clinical pharmacology

There are no significant concerns regarding the PK and PD of raltegravir 1200 mg QD.

2.5. Clinical efficacy

2.5.1. Main study

The efficacy of this new dose strength and dosing schedule was evaluated in a single study (292 - ONCEMRK)

Study Title: *A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Reformulated Raltegravir 1200 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Each in Combination With TRUVADA, in Treatment- Naïve HIV-1 Infected Subjects*

Methods

A Phase 3, multicentre, double-blind, randomised, active comparator controlled clinical study to evaluated the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID, each in combination with TRUVADA, was conducted in treatment-naïve HIV-1 infected subjects.

Study Participants

HIV-infected (RNA ≥ 1000 copies/mL) subjects who had never received antiretroviral therapy were included in the study. Subjects with documented HIV resistance to raltegravir or the NRTI backbone (tenofovir and emtricitabine) were excluded.

Endpoints

The primary endpoint was the proportion of subjects achieving HIV-1 RNA (Ribonucleic acid) < 40 copies/mL at Week 48.

Secondary endpoints

- CD4 cell counts

CD4 cell counts were determined at Screening, Randomisation (Day 1), Weeks 24, 48, 72, and 96, virologic failure confirmation, early discontinuation, and at the 14-day post-therapy follow-up. CD4 cell count determinations were performed by the central laboratory according to its standard procedures.

- Time to virologic response (TVR)
- Time to loss of virologic response (TLOVR).
- The proportion of subjects achieving HIV-1 RNA <50 copies/mL
- The proportion of subjects achieving HIV-1 RNA <200 copies/mL

Pharmacokinetic endpoints

- Raltegravir concentrations in all samples from an individual subject

- Raltegravir concentrations in all samples for an individual subject collected between 22 and 26 hours post-dose for the QD arm and between 11 and 13 hours post-dose for the BID arm of the study
- Minimum concentration value of all samples for an individual subject

Sample size

The sample size calculation was based on the following assumptions: an overall one-sided 2.5% significance level, 90% power, a true response rate of 85% at Week 48 for raltegravir 400 mg b.i.d. arm and no larger than 1% lower response rate for the for reformulated raltegravir 1200 mg q.d. arm using the NC=F approach as defined by the FDA "snapshot" approach, and a non-inferiority margin of 10%. The study was also powered to declare, with 95% confidence, that the true difference between treatment groups is no more than 10.0 percentage points for a reasonably common adverse experience which occurs in 20% of subjects receiving either reformulated raltegravir 1200 mg q.d. or raltegravir 400 mg b.i.d., each in combination therapy with TRUVADA.

A total of 802 subjects were randomised in a 2:1 ratio to received Reformulated Raltegravir 1200 mg once daily (q.d.) + TRUVADA q.d (Group 1, n=533) or Raltegravir 400 mg twice daily (b.i.d.) + TRUVADA™ q.d (Group 2, n=269).

The Full Analysis Set (FAS) population consisted of all randomised subjects who:

- received at least one dose of study treatment, and
- had baseline data for those analyses that require baseline data.

The per-protocol population was initially not defined. Therefore the applicant was requested to provide a PP definition retrospectively which is as follows:

The PP population excludes subjects due to important deviations from the protocol that may substantially affect or confound the results of the primary efficacy endpoint(s). Since these criteria were not pre-identified, the Applicant developed these criteria based on information about PP analyses gathered from ICH regulatory guidance [Ref. 5.4: 03RCZH], recent publications for HIV integrase inhibitors (dolutegravir, elvitegravir) [Ref. 5.4: 03TFV3] [Ref. 5.4: 03WQHQ] [Ref. 5.4: 04MGY8] [Ref. 5.4: 042KWT] [Ref. 5.4: 04MGYH] [Ref. 5.4: 04F2P3] and the company's anti-infective studies. Three high-level categories of exclusion were selected as described below: 1) Discontinuation for reasons not related to treatment; 2) Non-compliance with study medication; and 3) Identified major protocol deviations that have the potential to impact efficacy.

One interim analysis was performed for the sole purpose of stopping the study in the event of a lack of efficacy (futility) on 30 June 2015. The interim analysis was performed when approximately 375 subjects randomised in the study either completed the Week 24 visit or discontinued before Week 24.

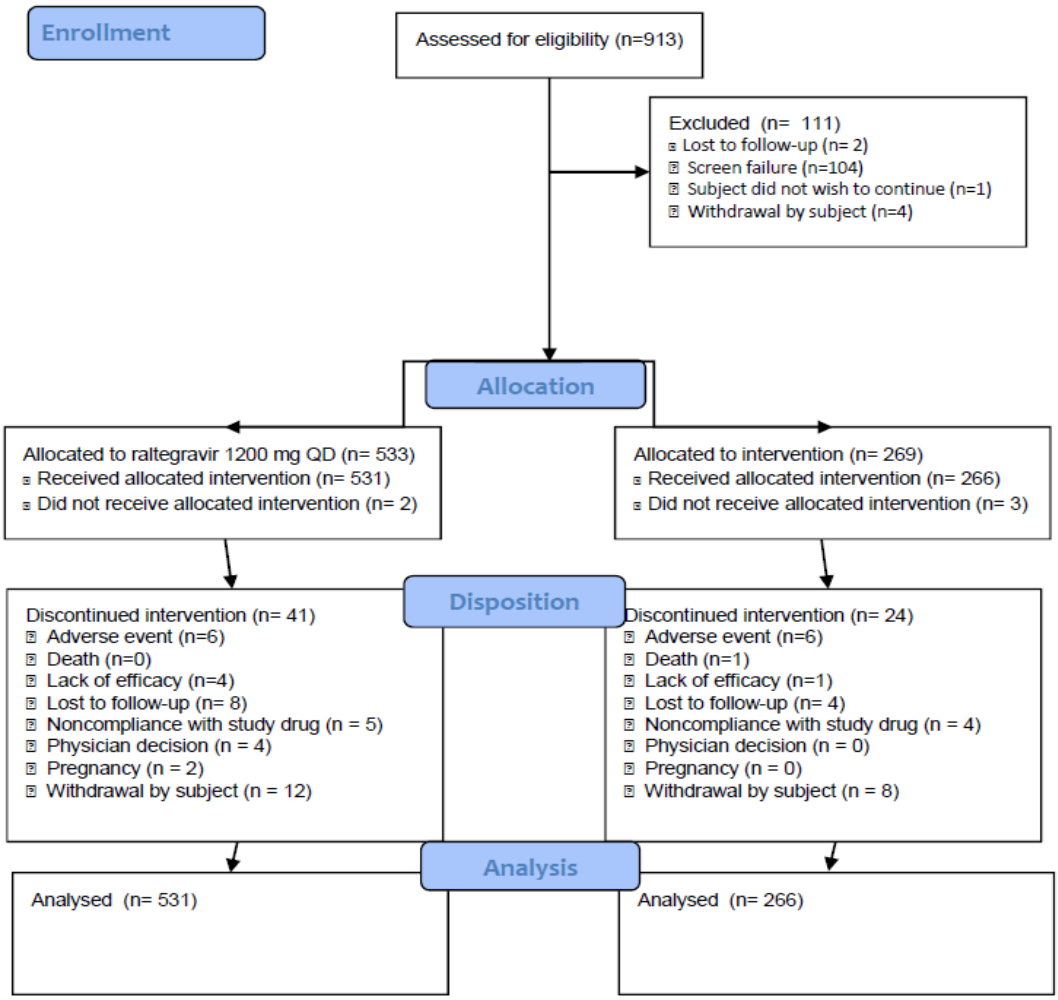
Primary analysis:

The difference in proportions of subjects achieving HIV-1 RNA < 40 copies / mL between treatment groups and the associated 95% confidence interval was calculated using stratum-adjusted Mantel- Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 copies/mL or HIV-1 RNA >100,000 copies/mL). All missing data were treated as failures regardless of the reason. Reformulated raltegravir 1200 mg q.d. was concluded non-inferior to raltegravir 400 mg b.i.d., each in combination therapy with TRUVADA, if the lower bound of the two-sided 95% CI for

the difference in proportion of subjects with HIV-1 RNA<40 copies/mL at Week 48 (reformulated raltegravir 1200 mg q.d. minus raltegravir 400 mg b.i.d.) was greater than -10 percentage points.

Results

Participant flow



Primary efficacy endpoint

The proportion of subjects achieving HIV RNA <40 copies/mL at Week 48 by the FDA Snapshot approach was 88.9% and 88.3% for the raltegravir 1200 mg QD and 400 mg BID groups, respectively. The treatment difference between the raltegravir 1200 mg QD group and 400 mg BID was 0.510%, 95% CI: (-4.204, 5.223). Therefore raltegravir 1200 mg QD group was demonstrated to be non-inferior to raltegravir 400 mg BID.

For the PP population, using the FDA snapshot approach (NC=F) for missing data, similarly high proportions of subjects achieved HIV-1 RNA <40 copies/mL at Week 48 in the QD and BID treatment groups: 93.2%

(455/488) versus 91.3% (232/254), respectively, with a treatment difference [95% CI] of 1.891% [-2.249, 6.032]. This demonstrates the non-inferiority of QD versus BID given the lower bound of the 95% CI is greater than -10%.

CD4 cell counts

At Week 48, the mean change from baseline in CD4 cells (cells/mm3)(95% CI) was 232.0 (214.6, 249.4) and 234.1 (212.8, 255.3) in the QD and BID groups, respectively.

The 48 week efficacy results are shown in Table 7.

Table 3. 48 Weeks efficacy results

ONCEMRK Study	**48 Weeks**	
Parameter	Raltegravir 600 mg (1,200 mg once daily) (N=531)	Raltegravir 400 mg twice daily (N=266)
Percent HIV-RNA < 40 copies/ml (95 % CI)		
All patients†	88.9 (85.9, 91.4)	88.3 (83.9, 91.9)
Baseline Characteristic‡		
HIV-RNA >100,000 copies/ml	86.7 (80.0, 91.8)	83.8 (73.4, 91.3)
≤100,000 copies/ml	97.2 (94.9, 98.7)	97.7 (94.3, 99.4)
CD4-count≤200 cells/mm^3	85.1 (74.3, 92.6)	87.9 (71.8, 96.6)
> 200cells/mm^3	95.6 (93.2, 97.3)	94.5 (90.6, 97.1)
Viral Subtype Clade B	94.6 (91.4, 96.8)	93.7 (89.0, 96.8)
Non-Clade B	93.6 (89.1, 96.6)	93.2 (84.9, 97.8)
Mean CD4 Cell Change (95 % CI), cells/mm^3		
All patients‡	232 (215, 249)	234 (213, 255)
Baseline Characteristic‡		
HIV-RNA > 100,000 copies/ml	276 (245, 308)	256 (218, 294)
≤ 100,000 copies/ml	214 (194, 235)	225 (199, 251)
CD4 count ≤ 200 cells/mm^3	209 (176, 243)	209 (172, 245)
>200 cells/mm^3	235 (216, 255)	238 (214, 262)
Viral Subtype Clade B	232 (209, 254)	240 (213, 266)
Non-Clade B	233 (205, 261)	226 (191, 261)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 40 copies/ml. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

Raltegravir 1,200 mg QD and raltegravir 400 mg BID were administered with emtricitabine (+) tenofovir disoproxil fumarate.

Protocol Defined Virologic Failure and Virologic Resistance (PDVF)

At Week 48, 36/531 (6.8%) subjects in the raltegravir QD group and 18/266 (6.8%) subjects in the raltegravir BID group were identified as PDVFs. In both treatment groups it would appear that half of the PDVFs were non-responders and the other half were rebounders.

It should be noted that in the raltegravir QD group, 27 of the 36 subjects (75.0%) who met PDVF criteria later suppressed below 40 copies/mL. 55.6% of these 36 subjects were considered successes at the Week 48

primary analysis. In the BID group, similarly, 13 of the 18 subjects (72.2%) later suppressed (44.4%) were considered successes at the Week 48 primary analysis.

Specimens from 14 subjects in the QD group and 3 subjects in the BID group with protocol-defined virologic failure were subjected to resistance testing.

The overall rate of resistance to any agent among subjects in the raltegravir QD group was 0.9% i.e. (5/531 of the subjects). All 5 had resistance to raltegravir and/or emtricitabine (FTC): 4 of the 5 had resistance to both raltegravir and FTC, and 1 had resistance to FTC only. The 4 subjects with raltegravir and FTC resistance had integrase mutations in N155H/I203M, V151I/N155H, N155H, L74M/E92Q as well as RT mutations in M184, either M184V or M184M/I/V. The subject with the L74M/E92Q mutation discontinued the study for lack of efficacy; this subject's HIV RNA levels were suppressed to <40 copies/mL at the 14-day follow-up visit. The subject with FTC resistance only had M184V and V118I mutations; this subject remained on study treatment and HIV RNA was re-suppressed to <40 copies/mL at Weeks 36 and 48.

No TDF mutations were observed. Among the 3 subjects in the BID group with virologic failure who had resistance testing performed, no raltegravir mutations were found. In all subjects with resistance mutations, compliance was at least 94%.

Overall it is considered that the resistance rate and pattern were similar to those described previously in the Phase 2 and 3 clinical studies of raltegravir BID conducted in treatment-naïve and treatment experienced subjects

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4. Summary of efficacy for trial P292

Title: A Phase 3, multicentre, double-blind, randomised, active comparator controlled clinical study which evaluated the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID, each in combination with TRUVADA™, in treatment-naïve HIV-1 infected subjects			
Study identifier	**P292**		
Design	Randomised, active comparator controlled, double-blind, multicentre		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks Not applicable 48 weeks
Hypothesis	**Primary Hypothesis** 1. Reformulated raltegravir 1200 mg QD is non-inferior to raltegravir 400 mg BID, each in combination therapy with TRUVADA™, as assessed by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48. **Secondary Hypothesis** 2. Reformulated raltegravir 1200 mg QD is non-inferior to raltegravir 400 mg BID, each in combination with TRUVADA™, as assessed by proportion of subjects achieving HIV-1 RNA <40 copies/ml at Week 96.		
Treatments groups	Raltegravir 1200 mg once daily (QD) + TRUVADA™ QD		1200 mg once daily (QD) for 48 weeks. **531 Subjects**
	Raltegravir 400 mg twice daily (BID) + TRUVADA™ QD		400 mg twice daily (BID for 48 weeks. **266 subjects**
Endpoints and definitions	Primary efficacy endpoint	HIV-1 RNA	The proportion of subjects achieving HIV-1 RNA < 40 copies/mL at Week 48

	Secondary efficacy endpoint	CD4	Change from baseline in CD4 count at Week 48
Database lock	10 February 2016		
Results and Analysis			
Analysis description	**Primary Analysis** HIV-1 RNA Statistical methodology: The primary hypothesis on antiretroviral activity was assessed by the percentage of subjects achieving plasma HIV RNA <40 copies/mL at Week 48. Raltegravir QD was concluded to be non-inferior to raltegravir BID if the lower bound of the two-sided exact 95% CI for the difference in response rate (raltegravir QD – raltegravir BID) remained above -10 percentage points. The NC=F approach as defined by FDA "snapshot" approach was used as the primary approach to analysis with respect to the proportion of subjects with virologic response (HIV-1 RNA <40 copies/mL). All missing data were treated as failures regardless of the reason.		
Analysis population and time point description	The Full Analysis Set (FAS) population: all randomized subjects who received at least one dose of study treatment and had baseline data for those analyses that require baseline data.		
Descriptive statistics and estimate variability	Treatment group	Raltegravir 1200 mg once daily (QD)	Raltegravir 400 mg twice daily (BID)
	Number of subject	531 (FAS)	266(FAS)
	The proportion of subjects achieving HIV-1 RNA < 40 copies/mL at Week 48	472 / 531 (88.9)	235 / 266 (88.3)
	95% confidence interval	0. 510 (-4. 204, 5.223)	
Analysis description	**<Secondary analysis** CD4 Statistical methodology: The treatment difference of changes in CD4 cell counts at time points of interest was estimated between the two treatment groups. However, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, magnitude and direction of the CD4 changes seen in each treatment arm. The OF approach was used for the calculations of change from baseline in CD4 cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.		
Descriptive statistics and estimate variability	Treatment group	Raltegravir 1200 mg once daily (QD)	Raltegravir 400 mg twice daily (BID)
	Change from Baseline in CD4 Cell Count (cells/mm3)	232.0 (214.6, 249.4)	234.1 (212.8, 255.3)
	95% confidence interval	- 2.1	(-30.9 , 26.7)

2.5.2. Discussion on clinical efficacy

This application concerns the use of two tablets of raltegravir 600mg film-coated tablet formulation taken once a day (1200mg QD) in combination with other antiretroviral agents for the treatment of HIV-1 infection. The intention is to simplify dosing of raltegravir by providing once daily dosing.

One phase III clinical study which evaluated the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) in comparison to raltegravir 400 mg BID, each in combination with TRUVADA™, in treatment-naïve HIV-1 infected subjects was provided in support of this application.

Design and conduct of clinical studies

In general, the design of the study including the patient selection criteria, statistical method, the endpoints and choice of comparator is acceptable. For the primary outcome, the cut-off of <40copies/ml at 48 weeks was used due to the sensitivity of the Abbott Real Time HIV-1 assay. This was considered acceptable. Raltegravir 400mg b.i.d is approved for use in treatment-naïve and treatment experienced patients and therefore acceptable as a comparator.

In the statistical analysis, the NC=F approach as defined by FDA "snapshot" approach was used as the primary approach to analysis was the proportion of subjects with virologic response. The sensitivity analysis was performed using the Observed Failure (OF) approach. Both approaches were considered acceptable.

The primary outcome was based only on the FAS. However since this is a non-inferiority study, the outcome should have been based on both the FAS and PP populations. Therefore the PP was retrospectively defined.

There were a number of protocol deviations including GCP non-compliance for which a GCP inspection was triggered. The results of the triggered inspection d showed no critical findings. However there were a number of major and minor findings with respect to eDiary completion and the reliability of the data to assess compliance as per the protocol definition.

Efficacy data and additional analyses

The proportion of subjects achieving HIV RNA <40 copies/mL at Week 48 by the FDA Snapshot approach was 88.9% and 88.3% for the raltegravir 1200 mg QD and 400 mg BID groups, respectively. The treatment different was 0.5 95% CI (-4.2 to 5.2). Therefore Raltegravir 1200mg QD was demonstrated to be non-inferior to Raltegravir b.i.d for the FAS

For the PP population, using the FDA snapshot approach (NC=F) for missing data, similarly high proportions of subjects achieved HIV-1 RNA <40 copies/mL at Week 48 in the QD and BID treatment groups: 93.2% (455/488) versus 91.3% (232/254), respectively, with a treatment difference [95% CI] of 1.891% [-2.249, 6.032]. This demonstrates the non-inferiority of QD versus BID given the lower bound of the 95% CI is greater than -10%.

In terms of secondary endpoints in particular CD4 counts, time to virologic response (TVR), time to loss of virologic response (TLOVR), The proportion of subjects achieving HIV-1 RNA <50 copies/mL and the proportion of subjects achieving HIV-1 RNA <200 copies/mL, the results for Raltegravir 1200mg QD were demonstrated to be comparable to Raltegravir 400mg b.i.d.

2.5.3. Conclusions on the clinical efficacy

Raltegravir 1200mg QD has been demonstrated to be non-inferior to Raltegravir bid in achieving HIV-1 RNA < 40 copies/mL at week 48 using the NC=F approach as defined by FDA "snapshot" approach and the Observed Failure (OF) approach for the FAS and PP population. The benefit risk for the proposed new posology is considered to be positive.

2.6. Clinical safety

Patient exposure

One hundred and thirty-three (133) subjects (39 female; 94 male) received at least one dose of raltegravir 1200 mg or 1800 mg QD in six Phase 1 studies (PN290, PN291, PN293, PN812, PN823 and PN824).

In the phase III study PN 292, 531 subjects received raltegravir 1200 mg QD and 266 subjects received raltegravir 400 mg BID for 48 weeks.

Adverse events

In the phase I studies, the most commonly reported adverse events (those occurring at an incidence ≥ 5%) for raltegravir alone were: headache (15%), hypertension (6.8%), myalgia (6%), and abdominal pain (5.3%), and for raltegravir + other were: diarrhoea (6%) and upper respiratory tract infection (6%).

In study PN 292, the proportions of subjects with AEs and with drug-related AEs in the QD group were similar to those in the BID group. The frequency of individual clinical AE preferred terms was similar in both treatment groups.

The most frequently reported clinical AEs (reported in ≥ 10% of subjects in one or more treatment groups), were: headache (13.4%, 10.9%), nausea (11.3%, 9.8%) and diarrhoea (10.9%, 11.3%). The most frequently reported (incidence >2%) drug-related AEs in either group (shown as % for QD, % for BID) were nausea (7.3%, 6.8%), headache (3.0%, 4.5%), and dizziness (2.3%, 3.0%)

Serious adverse event/deaths/other significant events

There were 3 fatal AEs in the study: tuberculosis and immunoblastic lymphoma in the QD group, and AIDS (worsening) in the BID group. Each of these AEs was early onset (by Day36 of the study) and may represent immune reconstitution system (IRS), although not reported as such by the investigator. The case of tuberculosis occurred in a subject with prior pulmonary TB, the case of immunoblastic lymphoma was newly diagnosed in the region of the kidney in a subject with lumbar pain at study entry, and the case of AIDS presented as progression of cryptococcal meningitis in a subject reported as having inadequately treated prior cryptococcal meningitis. None of these fatal adverse events was considered to be drug related

Serious drug-related clinical AEs were very infrequent (1/531 [0.2%] QD; 2/266 [0.8%] BID). The 1 serious drug-related AE in the QD group was headache, and was considered related to TRUVADATM and not raltegravir. The 2 serious drug-related AEs in the BID group included a transient increase in RNA (drug ineffective), and vomiting considered related to an overdose (2 extra tablets of placebo). No subjects discontinued from the study due to serious drug-related adverse events.

Clinical AEs leading to discontinuation (0.8% QD, 2.3% BID) or clinical AEs associated with IRS (2.1% QD, 1.1% BID) or AIDS defining condition (1.3% QD, 2.3% BID) occurred at similar and low frequencies in both treatment groups.

Laboratory findings

The frequencies of treatment-emergent laboratory abnormalities were similar for raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID Laboratory adverse events (7.0% QD; 11.3% BID) and drug-related laboratory adverse event (1.5% QD; 1.5% BID) were reported at low and comparable frequencies in the raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID groups.

Of the tests performed in routine monitoring, the most frequently (≥ 2% of subjects in one or more treatment groups) reported laboratory adverse events, regardless of drug relationship, were blood creatine phosphokinase increased (3.4%, 6.4%), and AST increased (2.6%, 1.9%) in the QD and BID groups, respectively.

Overall the frequencies of Grade 3 and 4 laboratory abnormalities were similar in the two groups: AST (8/530 QD group, 1/266 BID group), ALT (7/530 QD group, 1/266 BID group), and CPK (16/530 QD group, 11/266 BID group) occurred at similar frequencies in both treatment groups. Grade 3 or 4 ALT elevations occurred concurrently with Grade 2, 3 or 4 AST in a number of subjects in both groups (7/530 QD group and 1/266 BID group. In most cases, Grade 3 or 4 ALT elevations (with or without AST elevations) were self-limited and did not recur or require treatment interruption or had alternative aetiologies, such as viral hepatitis or use of hepatotoxic drugs.

Of the 7 cases of ALT elevations to Grade 3 or above in the QD group; three cases were associated with viral hepatitis – 2 with acute hepatitis C infection (which, in one case, led to discontinuation), and 1 with flare of hepatitis B infection.

Grade 3 or 4 CPK elevations occurred concurrently with Grade 2, 3, or 4 AST elevations in a number of subjects in both groups (6/530 [0.7%] QD; 4/266 [0.4%]). In most cases, Grade 3 or 4 CPK elevations (with or without AST elevations) were self-limited and did not recur or require treatment interruption. There were no cases associated with significant muscular conditions such as myositis or rhabdomyolysis. One subject in the QD group with Grade 3 or 4 CPK was discontinued due to recurrent CPK elevation without any associated clinical findings.

While Grade 3 and 4 lipase elevations were observed in both groups (13/530 [2.4%] QD; 1/266 [0.4%]), this was generally clinically silent, other than one subject in the QD group who had Grade 3 lipase with a concurrent diagnosis of pancreatitis, which persisted after resolution of the elevated lipase. No specific symptomatology was reported, no imaging was performed and amylase was not reported.

Safety in special populations

Adverse events were generally similar in patient sub-groups based on gender, age, ethnicity and race although there were very small sample sizes for some categories.

The safety profile of raltegravir QD was not affected by the presence of chronic hepatitis B and/or C virus co-infection, or by the use of gastric proton pump inhibitors and H2 blockers. Raltegravir 1200 mg QD (2 x 600 mg tablets) was generally well tolerated in these subgroups

Discontinuation due to adverse events

In study 292, it is noted that 4 (0.8%) and 6 (2.3%) subjects discontinued study therapy due to a clinical AE through Week 48 in the QD and BID groups respectively. These AEs included tuberculosis and other infections. There were no drug-related AEs that led to discontinuation in the QD group. In the BID group, 2 drug-related AEs led to discontinuation: early-onset drug eruption (resolved) and late-onset thrombocytopenia (ongoing).

Post marketing experience

Raltegravir 600mg tablets have not been previously marketed.

2.6.1. Discussion on clinical safety

The applicant has provided a scanty description of the safety profile. This is not considered to be a significant concern as the safety of raltegravir 400mg b.i.d is well known.

The most frequently reported clinical adverse events were headache, nausea and diarrhoea. The incidence of these comparable in the two treatment groups i.e. the 1200mg QD and 400mg bid groups.

Serious drug related adverse events are generally low in both treatment groups. However, there were three fatal adverse events tuberculosis and immunoblastic lymphoma in the QD group, and AIDS (worsening) in the BID group. These events were of early onset.

In terms of laboratory findings, the frequency of treatment-emergent laboratory abnormalities were similar for raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID.

Clinical AEs leading to discontinuation occurred at similar and low frequencies in both treatment groups.

2.6.2. Conclusions on the clinical safety

From the limited information provided by the applicant, there are no particular concerns to highlight. Raltegravir 1200 QD (600mg X 2) appears comparable to raltegravir 400mg b.i.d

2.6.3. PSUR cycle

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk Management Plan

Safety concerns

The list of safety concerns was updated as follows:

Important Identified Risks	• Immune reconstitution inflammatory syndrome • Drug resistance • Drug interaction with rifampin and other strong UGT1A1 inducers

	• Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD) • Serious Rash • Drug interaction with ~~magnesium and/or aluminum antacids~~.**metal Cation Containing Antacids** • Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis
Important Potential Risks	• Malignancies • Increase in liver enzymes • ~~Lipodystrophy/Fat maldistribution~~ • ~~Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis~~ • Depression, suicidal ideation, suicidal behaviors • Medication error related to 1) **potential substitution of pediatric formulations for the 400 mg film-coated tablet (pediatric formulations and the 400 mg film-coated tablet are not bioequivalent) and 2) potential substitution of one film-coated tablet) for the other**
Important Missing Information	• ~~Potential exposure during pregnancy~~ • ~~Long-term safety data~~ • ~~Populations studied~~ • ~~Populations insufficiently studied/not studied:~~ • ~~Exposure~~ **Safety in pregnant and/or lactating women** • **Safety in neonates less than 4 weeks of age** • ~~Exposure~~ **Safety in elderly patients** • ~~Exposure~~ **Safety in patients with severe hepatic impairment**

Pharmacovigilance plan

No new Pharmacovigilance activity has been added. Some completed studies have been removed from the Summary of the Pharmacovigilance Plan which now looks as follows:

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
Observational Studies				
Collaboration with the D:A:D Cohort Study (Category 3)	Along with other MAHs, the MAH is currently supporting the D:A:D cohort to monitor the safety of ARTs in Europe.	Monitored risks include cardiovascular risk; however, the study outcomes are not specific to raltegravir.	Ongoing	The MAH will support the collaboration until 2017 at which time the obligation will be completed.
Clinical Studies				
Study 022 (Category 3)	Evaluation of safety, PK and efficacy in pediatric	Long term safety data in	Ongoing	Submission by 31-Dec-2017

	patients 4 weeks to 18 years of age.	pediatric patients ages 4 weeks to 18 years.		(Final Week 240 CSR)
Study 080 (Neonatal study) (Category 3)	Evaluation of safety and PK in HIV-1 exposed neoates.	Exposure in neonates less than 4 weeks of age	Ongoing	Submission by 30-Sep-2017
Registry				
Antiretroviral Pregnancy Registry (Category 3)	The APR is an international collaborative project to monitor reported exposures to antiretroviral drugs during pregnancy. The Registry is designed to provide an early signal of teratogenicity with prenatal use of the drugs monitored through the Registry	Exposure during pregnancy	Ongoing	Provided every 6 months

Risk minimisation measures

The Summary Table of Risk Minimization Measures was updated as follows:

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
IRIS	Listed as class labeling warning in Section 4.4 and 4.8 of the SmPC. Package leaflet—Section 2, What you need to know before you take Isentress and Section 4, Possible side effects	None
Drug resistance	Listed under SmPC Sections 4.4 and 5.1. Package leaflet—Section 3, How to take Isentress.	None
Drug interaction with rifampin and other strong UGT1A1 inducers	Listed under SmPC Sections 4.4 and 4.5. Package leaflet—Section 2, What you need to know before you take Isentress	None
Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)	Listed under SmPC Sections 4.4, 4.5 and 5.2.	None
Serious rash	Listed under SmPC Section 4.4 and 4.8. Package leaflet—Section 2, What you need to know before you take Isentress and Section 4, Possible side effects	None

The Summary Table of Risk Minimization Measures was updated as follows:

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Drug interaction with ~~magnesium and/or aluminum~~ **metal cation containing** antacids	Listed under SmPC Section 4.4 and 4.5 Package leaflet—Section 2, What you need to know before you take Isentress	None
Increase in ~~liver enzymes~~ **CPK with clinical manifestations; myopathy, rhabdomyolysis**	Listed under SmPC ~~Section~~ **Sections 4.4 and 4.8**. Package leaflet—Section 2, What you need to know before you take Isentress and Section 4, Possible side effects	None
Important Potential Risks		
~~Lipodystrophy/Fat Maldistribution~~ **Malignancies**	Listed under SmPC Section 4.8 Package leaflet—Section 4, Possible side effects	None
Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis **liver enzymes**	Listed under SmPC ~~Sections 4.4 and~~ **Section** 4.8. Package leaflet—Section 2, What you need to know before you take Isentress and Section 4, Possible side effects	None
Depression, Suicidal ideation, Suicidal behaviors	Listed under SmPC Section 4.4 and 4.8 Package leaflet—Section 2, What you need to know before you take Isentress and Section 4, Possible side effects	None
Medication Error related to 1) potential substitution of **the** pediatric formulations for ~~non-chewable tablets~~ **the 400 mg film-coated tablet** (given pediatric formulations and ~~non-chewable tablets~~ **the 400mg film-coated tablet** are not bioequivalent) **2) potential substitution of one film-coated tablet for the other**	Listed in SmPC Section 4.2, Posology and method of administration, of the SPC. Package leaflet—Section 3, How to take Isentress	None
Important Missing Information		
Safety in pregnant and lactating women.	Listed in SmPC Section 4.6. Package leaflet—Section 2, What you need to know before you take Isentress	None
Safety in neonates less than 4 weeks of age	SmPC Section 4.2 notes that safety and efficacy has not been established in patients below 4 weeks of age. Lack of PK in this	None

The Summary Table of Risk Minimization Measures was updated as follows:

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	population is discussed in Section 5.2. Package leaflet—Section 2, What you need to know before you take Isentress	
Safety in elderly patients	SmPC Section 4.2 includes information about limited information in the elderly. PK information is included in Section 5.2.	None
Safety in patients with severe hepatic impairment	SmPC Section 4.2 includes dosing recommendations in patients with hepatic impairment. The SmPC also includes language in Section 4.4 related to patients with severe hepatic impairment. Package leaflet—Section 2, What you need to know before you take Isentress	None

No additional risk minimisation measures have been proposed as part of this procedure. Amendments have been made to distinguish the 600mg strength, namely the font size of the “600mg” text within the coloured/ teal bars on the package are increased and a statement on the non-interchangeability of the product has been added. In addition, the following statement has been added “Two tablets once a day”. Furthermore, the Applicant committed to include the statement on non-interchangeability of the products throughout the range of Isentress product.

The Applicant committed to improve the packaging of their existing products using a similar approach as seen with the 600mg strength packaging, such as with use of larger colour bars and increased font size of the strength within the colour bars.

Conclusion

The CHMP and PRAC considered that the risk management plan version 11.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HIV is the virus that causes the Acquired Immune Deficiency Syndrome (AIDS). HIV infects and leads to a depletion of immune cells (CD4 + cells). As the CD4-positive cells are depleted, the host becomes increasingly susceptible to a variety of opportunistic pathogens and immune deficiency related diseases.

ISENTRESS® is currently approved for the treatment of HIV-1 infection in patients 4 weeks of age or older. It is dosed twice daily (BID) in all current formulations. It is available and marketed as a 400 mg film-coated tablet formulation for patients weighing at least 25 kg, as a chewable tablet formulation in 100 mg (scored) and 25 mg strengths for patients weighing at least 10 kg, and as granules for suspension in patients weighing at least 3 kg. This particular application concerns a 600 mg film-coated tablet formulation which has been developed for use as two tablets (1200 mg) taken once daily (QD). The intention is to simplify and provide a more convenient treatment option by providing a once daily dosing for HIV-1 patients both infected treatment-naïve patients and patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID as it is considered that this might facilitate and improve the probability of achieving and maintaining optimal efficacy.

3.1.2. Available therapies and unmet medical need

A number of agents are licensed to treat HIV-1 infection which include 6 distinct mechanistic classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors (EIs), integrase strand transfer inhibitors (InSTI; also commonly referred to as integrase inhibitors), and pharmacokinetic enhancers. Current guidelines recommend 2 NRTIs and a third agent, generally of the InSTI or PI class.

HIV infection requires life-long therapy, and patients must adhere to treatment to avoid virologic failure and the development of resistance. HIV-infected patients often have concomitant medical conditions, necessitating the use of multiple medications for non-HIV related conditions. Thus, any measure to simplify HIV treatment increases the potential for improved adherence and overall therapeutic success.

3.1.3. Main clinical studies

The pivotal study was a Phase 3, multicentre, double-blind, randomised, active comparator controlled clinical study which evaluated the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID, each in combination with TRUVADA, in treatment-naïve HIV-1 infected subjects.

A total of 802 subjects were randomised in a 2:1 ratio to Raltegravir 1200 mg once daily (QD; 2 x 600 mg tablets) or Raltegravir 400 mg twice daily (BID; 1 x 400 mg tablet in combination with TRUVADA™. Randomisation was stratified by RNA levels at screening and hepatitis B/C status, using centralised randomisation.

The study was designed to evaluate the antiretroviral activity of reformulated raltegravir 1200 mg QD, compared to raltegravir 400 mg BID, each in combination therapy with TRUVADA, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48. The FDA snapshot approach was used to determine virologic response (HIV RNA < 40 copies/mL) at Week 48.

3.2. Favourable effects

The primary analysis was based on the FAS (n=797), which included all randomised subjects who were treated. Similar rates for sustained virologic success were achieved through Week 48 in both treatment groups. Estimates of the difference (95% CI) in the proportions of subjects with HIV RNA < 40 copies / mL at Week 48, based on the FDA snapshot approach was 0.510 (-4.204, 5.223). The lower limit of the 95% confidence interval excluded the pre-defined margin of -10%. For the PP population, using the FDA snapshot approach (NC=F) for missing data, similarly high proportions of subjects achieved HIV-1 RNA <40 copies/mL at Week 48 in the QD and BID treatment groups: 93.2% (455/488) versus 91.3% (232/254), respectively, with a treatment difference [95% CI] of 1.891% [-2.249, 6.032]. This demonstrates the non-inferiority of QD versus BID given the lower bound of the 95% CI is greater than -10%.

In terms of secondary endpoints in particular CD4 counts, time to virologic response (TVR), time to loss of virologic response (TLOVR), The proportion of subjects achieving HIV-1 RNA <50 copies/mL and the proportion of subjects achieving HIV-1 RNA <200 copies/mL, the results for Raltegravir 1200mg QD were demonstrated to be comparable to Raltegravir 400mg b.i.d.

The results from the sensitivity and subgroup analyses are generally consistent with the primary analysis.

3.3. Uncertainties and limitations about favourable effects

The primary outcome has been based only on the FAS. However since this is a non-inferiority study, the outcome should have been based on both the FAS and PP populations. Therefore the PP population was defined retrospectively

Compliance with study treatment was good overall and the dropout rates were low and similar in both treatment groups (less than 10%). However, there were a number of protocol deviations including GCP non-compliance, assessment of efficacy, and violations of the entry criteria.

3.4. Unfavourable effects

The most frequently reported clinical adverse events were headache, nausea and diarrhoea. The incidence of these comparable in the two treatment groups i.e. the 1200mg QD and 400mg bid groups. The incidence of headache (13.4% in the 1200mg QD group and 10.9% in the 400mg bid group, nausea (11.3% in the 1200mg QD group and 9.8% in the 400mg bid group and diarrhoea (10.9% in the 1200mg QD group 11.3% in the 400mg bid group).

Serious drug related adverse events are generally low in both treatment groups. However, there were three fatal adverse events: tuberculosis and immunoblastic lymphoma in the QD group, and AIDS (worsening) in the BID group. These events were of early onset and probably IRS.

In general, adverse events were generally similar in patient sub-groups based on gender, age, ethnicity and race. Overall, the safety profile of raltegravir 1200 QD (600mg X 2) appear comparable to that of raltegravir 400mg b.i.d.

3.5. Uncertainties and limitations about unfavourable effects

There are no limitations and uncertainties about unfavourable effects that have an impact on the benefit-risk balance

3.6. Effects Table

Table 5. Effects Table for Isentress QD regimen

Effect	Short Description	Unit	Raltegravir 1200mg QD	Raltegravir 400mg bid	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary efficacy end-point	The proportion of subjects achieving HIV-1 RNA < 40 copies/mL at Week 48	%	88.9	88.3	Analysis and results based on the PP populations is lacking. There were a number of protocol deviations including GCP non-compliance, assessment of efficacy, and violations of the entry criteria.	Pivotal trial

Effect	Short Description	Unit	Raltegravir 1200mg QD	Raltegravir 400mg bid	Uncertainties/ Strength of evidence	References
Secondary efficacy endpoint	Change from Baseline in CD4 Cell Count (cells/mm3)	(cells /mm3)	232.0	234.1		Pivotal trial
Unfavourable Effects						
Headache	ADR most frequently reported	%	13.4%	10.9%	None	Pivotal trial
Nausea	ADR most frequently reported	%	11.3%	9.8%	None	Pivotal trial
Diarrhoea	ADR most frequently reported	%	10.9%	11.3%	None	Pivotal trial
Tuberculosis	?IRS		One subject	None	None	Pivotal trial
immunoblastic lymphoma	IRS		One subject	None	None	Pivotal trial
AIDS (worsening)	IRS		None	One subject	None	Pivotal trial

Abbreviations: IRS: Immuno-reconstitution syndrome

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Evidence of clinical efficacy is provided from a single pivotal study in treatment-naïve HIV infected subjects. The primary analysis was based on the FAS (n=797), which included all randomised subjects who were treated. Similar rates for sustained virologic success were achieved through Week 48 in both treatment groups. Estimates of the difference (95% CI) in the proportions of subjects with HIV RNA < 40 copies / mL at Week 48, based on the FDA snapshot approach was 0.510 (-4.204, 5.223). The lower limit of the 95% confidence interval excluded the pre-defined margin of -10% and was well away from the pre-defined non-inferiority margin. However since this is a non-inferiority study, the outcome should have been based on both the FAS and PP populations. Therefore the PP population will need to be defined retrospectively using a standard definition from published trials.

In terms of the adverse events these were generally low in both treatment groups and the adverse events were generally similar in patient sub-groups based on gender, age, ethnicity and race. Overall, the safety profile of raltegravir 1200 QD (600mg X 2) appear comparable to that of raltegravir 400mg b.i.d.

There are no significant concerns to note regarding the unfavourable effects that have a negative impact on the benefit risk of raltegravir 1200 QD.

3.7.2. Balance of benefits and risks

Raltegravir 1200mg QD has been demonstrated to be non-inferior to Raltegravir bid in achieving HIV-1 RNA < 40 copies/mL at week 48 using the NC=F approach as defined by FDA "snapshot" approach and the Observed Failure (OF) approach for the FAS and for the PP population. In terms of the adverse events, there are no significant concerns to note.

The benefit risk for the proposed new posology is considered to be positive.

3.8. Conclusions

The overall B/R of Isentress is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Isentress 600 mg film-coated tablets is favourable in the following indication:

Isentress 600 mg film coated tablets is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV 1) infection in adults, and paediatric patients weighing at least 40 kg (see sections 4.2, 4.4, 5.1 and 5.2).

The CHMP therefore recommends extension of the marketing authorisation for Isentress 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).

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.