15 December 2022
EMA/CHMP/116101/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Raltegravir Viatris

International non-proprietary name: raltegravir potassium

Procedure No. EMEA/H/C/005813/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AE	Adverse Event
ANSM	National Agency for the Safety of Medicine and Health Products
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area Under the plasma Concentration
$AUC_{0\text{-}inf}$	Area Under the plasma Concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area Under the plasma Concentration-time curve from time zero to t hours
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BLQ	Below Limit of Quantification
CEP	Certificate of Suitability
C_{max}	maximum plasma Concentration
CHMP	Committee for Human Medicine Products
CoA	Certificate of Analysis
CP	Centralised procedure
CRF	Case Report Form
CRO	Certified Research Organisation
CV	Coefficient of Variation
eAF	electronic Application Forms
EDQM	The European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
ICP-MS	Inductively coupled plasma mass spectrometry
IEC	Independent Ethics Committee
IPC	In-Process Control
IR	Infrared spectroscopy
IS	Internal Standard
ISR	Incurred Sample Reanalysis
ISTD	Internal Standard
K_3EDTA	Tripotassium Ethylenediaminetetraacetic Acid
KF	Karl Fisher
LC	Liquid Chromatography
LDPE	low density polyethylene
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
LOQ	List of Questions
LS	Least Squares
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	British National Competent Authority
MS	Mass Spectrometry
NLS	not less than
NMR	Nuclear magnetic resonance spectroscopy
NMT	not more than
Ph. Eur	European Pharmacopoeia
PSD	Particle Size Distribution
PVC	polyvinyl chloride
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RH	Relative Humidity

Rpm	revolutions per minute
RSD	Relative Standard Deviation
SD	Standard Deviation
SmPC / SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TAMC	Total Aerobic Microbial Count
T/R	Test/Reference
T_{max}	Time for maximum concentration (* median, range)
$T_{1/2}$	terminal half-life
TYMC	Total Combined Yeasts/Moulds Count
ULOQ	Upper Limit of Quantification
UV	Ultraviolet
VR	Validation Report
XRD	X-Ray Diffraction

1. Recommendation

Note: *The Applicant withdrew their application for 400 mg strength after Day 120.*

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the generic application for Raltegravir Viatris 600 mg film-coated tablets in the treatment of human immunodeficiency virus (HIV-1) infection in adults, and paediatric patients weighing at least 40 kg, is not approvable since "major objections" have still been identified, which preclude a recommendation for marketing authorisation at the present time. The details of the major objections are provided in the List of Outstanding Issues.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

1.1. Questions to be posed to additional experts

Questions to be posed to MWP:

1.

a) Does the MWP consider the ANOVA model specified for the analysis of the pooled data set adequate? The assessment report mentions the factors used in the ANOVA model to be: study, sequence, treatment, subject (nested within the sequence*study), period (nested within the study), sequence*study interaction, and study*treatment interaction.

b) Does the MWP consider the intra-subject CV estimate (for the reference) from the pooled data analysis as appropriate? Is the estimator used the only and natural choice, or could there have been other (equally suitable) options?

2. Can the MWP elaborate on type-1-error control over the multiple BE-testing of Cmax (RALT-TBZ-1003, RALT-1-19208 and pooled analysis)? In particular, can a necessary coverage probability of the confidence interval resulting from the pooled analysis be specified? As a solution to this is expected to be controversial/infeasible, can a tipping point analysis for the pooled data setting be a reasonable approach to inform eventual decision making in such a generic application?

1.2. Inspection issues

None.

1.2.1. GMP inspection(s)

Not required.

1.2.2. GCP inspection(s)

Not required.

1.3. Similarity with authorised orphan medicinal products

Not applicable.

1.4. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

2.2. About the product

Raltegravir is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

The targeted indication for Raltegravir Viatris 600 mg film-coated tablets states as follows:

- *Raltegravir Viatris 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.*

The proposed posology states as follows:

- 600 mg: *In adults and paediatric patients (weighing at least 40 kg), the recommended dosage is 1,200 mg (two 600 mg tablets) once daily.*

Initially, the Applicant applied also for 400 mg strength. However, due to significant differences in formulation between the two strengths, the biowaiver was not acceptable and following D120 List of questions, the Applicant withdrew the application for the lower strength.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

To support this application, the Applicant submitted one bioequivalence study. The Applicant received CHMP Scientific Advice on 29 January 2021 pertinent to the following aspect:

- Biowaiver request for the lower (400 mg) strength
- Acceptance criteria for Cmax and AUC in the bioequivalence study for the 600 mg strength

The scientific advice was generally followed. The biowaiver for the lower 400 mg strength was requested, however due to significant differences in terms of composition and pharmacokinetics between 400 mg and 600 mg tablets of the reference product, the biowaiver for the lower 400 mg strength cannot be accepted, since the bioequivalence cannot be extrapolated to 400 mg strength. Therefore, the applicant continues with the authorisation procedure for 600 mg strength only.

2.4. General comments on compliance with GMP, GLP, GCP

No issues have been identified that specifically demand for an inspection.

At the time of submission valid GMP certificates for all proposed sites were available in EudraGMP database. Also, at the time of submission adequate QP declarations are provided.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(1) of Directive 2001/83/EC

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Isentress 600 mg film-coated tablets
- Marketing authorisation holder: Merck Sharp & Dohme
- Date of authorisation: 19.12.2007.
- Marketing authorisation granted by: EU
- Marketing authorisation number: EU/1/07/436/006-007

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

- Product name, strength, pharmaceutical form: Isentress 600 mg film-coated tablets
- Marketing authorisation holder: Merck Sharp & Dohme
- Date of authorisation: 19.12.2007.
- Marketing authorisation granted by: EU
- Marketing authorisation number: EU/1/07/436/006-007

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

- Product name, strength, pharmaceutical form: Isentress 600 mg film-coated tablets
- Marketing authorisation holder: Merck Sharp & Dohme
- Date of authorisation: 19.12.2007.
- Marketing authorisation granted by: EU
- Marketing authorisation number(s): EU/1/07/436/006-007
- Bioavailability study number(s): RALT-TZ-1003

2.5.2. Orphan designation

Not Applicable.

2.5.3. Similarity with orphan medicinal products

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

2.5.4. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.5. Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is film-coated tablets containing raltegravir potassium as active substance.

Each film-coated tablet contains 600 mg of raltegravir which correspond to 651.395 mg of raltegravir potassium.

Other ingredients are: calcium sulfate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate in tablet core and polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, yellow iron oxide (E172) and red iron oxide (E172) in tablet coating.

The product is available in OPA/Aluminium/PVC-Aluminium blister packs of 60 tablets and perforated unit dose blisters of 60 x 1, as well as in blue opaque High-Density Polyethylene (HDPE) bottles with desiccant and a blue opaque polypropylene (PP) screw cap in packs of 60 or 180 tablets.

The Ph. Eur., monograph for Raltegravir Tablets has been published in Supplement 9.8 (01/2022:2938) and implemented on 1 July 2019.

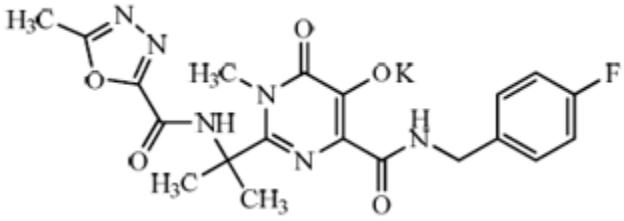
3.1.2. Active Substance

Raltegravir potassium is included in the European Pharmacopoeia (04/2018:2887, corrected in version 10.3).

The drug substance documentation used in this procedure is presented in the form of an Active Substance Master File / ASMF.

3.1.2.1. General Information

The active substance raltegravir potassium (INN) belongs to therapeutic category of anti-retroviral. Chemical name is: Potassium 4- [[(4-fluorophenyl) methyl] carbamoyl]-1-methyl-2 – [2-[(5-methyl-1,3,4- oxadiazol-2-yl)formamido]propan-2-yl]-6-oxo-1,6-dihydropyrimidin-5-olate corresponds to the molecular formula $C_{20}H_{20}FKN_6O_5$. It has a relative molecular mass of 482.5 g/mol and the following structure:



The active substance is a white off-white powder. Exhibits low solubility (BCS Class II) and solubility is pH-dependent (increases at high pH). It is slightly hygroscopic in nature, which is supported by data.

Raltegravir potassium contains neither asymmetric nor chiral carbon atom. It indicates that raltegravir potassium does not exhibit optical isomerism.

Raltegravir potassium exhibits polymorphism. It is demonstrated that the active substance manufacturer consistently produces the same form of active substance. The identification test of the polymorphic form by XRPD is included in the active substance specification. Stability of polymorph form is confirmed by 6 months at accelerated (25°C/60%RH) and 36 months at long-term conditions (5±3°C), supported by stability data presented in section S.7.3.

The material can be micronised by the active substance manufacturer as per the particle size requirement of drug product manufacturer. Confirmation is given that presented ASMF is applicable for milled/micronized raltegravir potassium.

3.1.2.2. Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the Restricted part of the ASMF. Information regarding starting materials, batch size and milling are adequately included in the AP-ASMF.

The manufacturing process of raltegravir potassium is presented.

No alternative steps and recovered solvents used in the manufacturing process of the API. Reprocess procedures are enclosed.

In-process controls have been adequately described. Critical process parameters and steps have been identified and acceptable.

The chemical structure of raltegravir potassium has been elucidated by UV, IR, Mass spectroscopic analysis, ^{1}H-NMR and ^{13}C NMR, Elemental analysis and XRD with representative spectra included in the documentation. Sufficient information is provided on elucidation of structure and other characteristics.

Detailed discussion on actual and potential impurities that are likely to arise during the synthesis have been provided and the mechanisms utilized for their control are presented.

Solvents used in the process are tested in the final substance at ICH Q3C limits.

According to enclosed data it can be concluded that the active substance is free from genotoxic impurities.

For elemental impurities risk assessment according to ICH Q3D provided. No risks were identified. Screening of elemental impurities by validated method was performed. Further controls in the API are deemed unnecessary.

The active substance manufacturer has provided adequate documentation and discussion regarding of the outcome of risk assessment on nitrosamines. It can be confirmed that there is no risk relating to nitrosamine impurities to be carried over by API in the drug product.

3.1.2.3. Specification(s)

The proposed drug substance specifications comply to in-house standards.

Additional tests for identification by XRD (included to identify the polymorphic form), residual solvents are included by the active substance manufacturer. The test parameters included in the specification are

generally in line with ICH Q6A. An omission of test for microbial purity is adequately justified. The reference of each in-house analytical method is included in the specification.

The in-house methods are adequately validated. It is confirmed that the HPLC method for related substances is stability indicating. Since the active substance manufacturer developed an in-house method for related substance, method equivalence with Ph. Eur. method is conducted. By validation was covering all the in-house impurities and those listed in Ph. Eur. monograph related to Applicant's specification. The obtained results shows that in-house method is more sensitive than Ph. Eur. method to quantify all the impurities. In-house validated method could be adopted for determination of related substances in raltegravir potassium.

Batch analysis data for 6 recent commercial batches are provided. All batches comply with the current Ph. Eur. monograph and with the additional proposed specification and demonstrate the consistent quality of material.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Raltegravir potassium is packed in white polyethylene bag (HMLDPE) heat sealed under vacuumised nitrogen. The primary packaging material complies with EC 10/2011 as amended, as well as with Ph. Eur. 3.1.3. and Ph. Eur. 3.2.2.

3.1.2.4. Stability

Stability data of 6 batches (manufactured at two of the active substance manufacturing sites) conducted at accelerated (25±2°C/60±% RH) and long-term conditions (5 ± 3°C), stored in the intended commercial package are available. Although some results for water content during the stability study were above Ph. Eur. limit, according to provided stability data all results after 36 months of storage comply with Ph. Eur. requirements. Based on the stability data presented, the active substance is stable during 36 months if stored in tight, light-resistant containers in between 2°C and 8°C.

The stability indicating nature of the in-house HPLC method for related substances are demonstrated by means of forced degradation study. According to the enclosed data it can be concluded that the API is not sensitive to light.

Drug substance related to additional data provided by Applicant only

The drug product manufacturer has provided data in sections S.4 and S.5.

Drug product manufacturer's specification for raltegravir potassium is identical to the active substance manufacturer's specification, with the addition of PSD testing.

Considering low solubility of API, the drug product manufacturer has established limits for particle size to be in line with the distribution of the particle size of the API batches that have been incorporated in the drug product batch that is used for the bio-equivalence study. Omission of microbial test is adequately justified.

The validated analytical procedures used by the drug product manufacturer to test raltegravir potassium drug substance are the same as those being followed by the drug substance manufacturer. Reference is given to the AP of the ASMF sections 3.2.S.4.2 and 3.2.S.4.3. In addition, the specification/test method followed at drug product manufacturing site has additional validated test for particle size.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three API batches tested by the drug product manufacturer according to the proposed specification has been presented. The results are within the proposed specification.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

The proposal for Raltegravir 400 mg film coated tablets is withdrawn from the CP procedure (EMEA/H/C/005813). Hence, all the dossier sections have been updated to remove the information associated with 400 mg strength. The overview provided below is related to the strength of 600 mg only.

Description of the product

Immediate release, film-coated tablets (solid oral dosage form)

Raltegravir film-coated Tablets 600 mg	:	A yellow colored, capsule shaped, convex beveled edge film coated tablet debossed with "RLT" on one side of the tablet and "M" on the other side. **Dimension:** Approximately 18.6 mm x 9.6 mm

Raltegravir 600 mg film-coated tablets are packaged in 2 different marketing packs i.e., either:

cold form blister pack comprising of cold forming material (OPA/Aluminium/PVC) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Blister strips will be placed in an outer cardboard carton.

Or in:

High density polyethylene (HDPE) bottle pack comprising of blue opaque HDPE bottle with blue opaque polypropylene (PP) screw closure with aluminium induction sealing liner wad along with a desiccant, either placed in an outer cardboard carton or provided without a carton.

Bulk pack comprises of tablets in a Low-Density Polyethylene (LDPE) bag. The LDPE bag is placed in an outer triple laminated bag along with desiccant (silica gel bags) in between the LDPE bag and outer triple laminated bag and sealed. The triple laminated bags are then placed in a suitable tertiary pack (i.e., Plastic drum /shipper).

Pharmaceutical development

The finished product has been developed to be a generic equivalent to the reference medicinal product Isentress 600 mg film-coated tablet. Consequently, the objective was to prepare a film-coated tablet being essentially similar to the reference medicinal product. Raltegravir Viatris 600 mg film-coated tablets have the same qualitative and quantitative composition in terms of active substance and is also of the same pharmaceutical form as the comparator product. Qualitative composition of the excipients in the test product is not identical as in the reference product. Since the composition is not identical to the reference product, the suitability of the dosage form and the excipients for the paediatric population has been discussed. Presented toxicological information has been reviewed by the non-clinical assessor with the conclusion that that the chosen excipients have no safety hazard to paediatric patient populations (weighing at least 40 kg) and are acceptable for use in the manufacture of Raltegravir 600 mg film-coated tablets.

Critical process parameters have been identified through systematic evaluation using risk assessment methodologies. Quality target product profile (QTPP) and critical quality attributes (CQAs) are used for drug product development. A summary of the knowledge gained throughout development experiments to

production scale associated with processing parameters and their impact on critical quality attributes of film-coated tablets is provided. The process compensates for the variability in the material attributes. A control strategy of the material attributes and process parameters are proposed which includes in-process controls and finished product specifications.

As per the QTPP the final formulation, pharmaceutical form and manufacturing process were selected. No overages are used in the drug product.

All selected excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

No polymorphic change has been detected during drug product manufacturing and stability testing. Polymorphic identification test by PXRD is included in drug product manufacturer`s API specification and only one drug substance crystalline polymorph form has been identified in the drug substance studies. It is acceptable that crystalline form is not controlled routinely during drug product manufacturing.

Comparison of impurity profiles of reference and test product has been presented. The presented results are comparable.

Raltegravir potassium exhibits low solubility (BCS Class II) and solubility is pH-dependent (increases at high pH). This is taken into account in the evaluation of suitability of the *in vitro* dissolution method and of the comparative dissolution profiles submitted for investigation of similarity.

Discussion regarding development of the dissolution method for routine testing is provided. Based on the data provided, the chosen dissolution method applied is not considered sufficiently discriminative at the proposed limits (for further information and conclusion regarding proposed dissolution limit, see below in point 3.1.3.3). Comparative dissolution studies have been performed between the test and the reference bio-batches according to QC method, as well as in multimedia (at pH 1 (0.1M hydrochloric acid), pH 4.5 acetate buffer and at pH 6.8 phosphate buffer).

From the presented data there are no differences in the manufacturing processes of the commercial product and clinical trial material.

A detailed information has been provided on the development of the manufacturing method. Each stage of the manufacturing process has been evaluated following a process development risk assessment.

The selected container closure systems are common for this dosage form. The container closure system is suitable for use based on development studies.

3.1.3.2. Manufacture of the product and process controls

Manufacturer of the drug product is located in India while testing and secondary packaging are performed in Europe

Raltegravir film-coated tablets manufacturing process consists of ten main steps: dispensing of raw materials, sifting, pre-compaction blending, compaction, milling and sifting, sifting of extra granular material, blending, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The overview of production process is provided, accompanied by a flow chart. The description of manufacturing process is in line with manufacturing process development provided under section P.2. Generally, the provided data are considered sufficient for manufacturing procedures of conventional solid oral dosage formulation.

The information provided on the method of manufacture and the controls applied is generally acceptable. Enclosed narrative description is found to be acceptable.
Three production validation scale batches of Raltegravir tablets of 600 mg have been manufactured (including BE batch) at the commercial site (validation batches are also included in the formal stability studies). Enclosed validation data are found to be satisfactory.

A bulk hold time for the film-coated tablets up to 12 months is proposed and this is supported by stability data on batches of each dosage strength packed in bulk packaging.

The expiration period of a batch is calculated in accordance with the EU guideline Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).

3.1.3.3. Product specification (s)

The specification for batch release and shelf-life for 600 mg is proposed. The specifications have been identified by a version and date of approval / effective date.

The specification for batch release and shelf-life includes tests for appearance and dimensions, identification (by two methods; HPLC and IR), assay, degradation products, dissolution, uniformity of dosage units (mass variation), water content and microbial limits as well as colorants identification. The proposed specifications include all relevant parameters to the dosage form. Hardness, average weight, and friability are tested as IPC during compression stage, this is considered sufficient.

Limits for uniformity of dosage units and microbiological quality are in line with the relevant Ph. Eur. monographs. The proposed limits for raltegravir assay throughout the shelf life of the product are acceptable without further justification. Limits for two specified impurities that have been found above qualification limit during stability testing were adequately supported by toxicological data and generally acceptable. Limits for other impurities are acceptable as well as limit for water (different limit in the release than in the shelf life specification).

The analytical procedures have been described in sufficient detail and are adequate to control the finished product on a routine basis. Appropriate validations of proposed in-house methods in line with ICH requirements are enclosed.

Batch analysis data of three scale batches have been presented. All batches are showing compliance to the current specifications and batch-to-batch consistency is confirmed.

Risk assessment for elemental impurities is performed according to ICH Q3D, based on the maximum daily intake of the drug product per day considering the total matrix weight of 2 tablets (calculated from the maximum daily dose of 1200 mg of raltegravir). Batch analysis data on 3 batches, using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

As per the updated EMA guideline (EMA/369136/2020 - Nitrosamine impurities in human medicinal products) requirement, the Applicant has assessed the possible presence of nitrates and nitrites i.e. the possibility of formation nitrosamines during synthesis of the drug substance, from excipients used in manufacturing of drug product, during drug product manufacturing, used equipment and packaging material, as well as environmental conditions and possible cross-contamination. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The selected container closer systems (HDPE bottle and blister packs) are common for this dosage form and blister packaging. Specifications, method of analysis and CoA's of all primary packaging materials as well as declarations of compliance, when relevant, with the EU Directive 10/2011 and amendments are provided. The materials comply with Ph. Eur. and EC requirements. Additionally, test for dimensions are included in HDPE container specification and drawings of the container closure systems presented. The adequate justification is enclosed regarding used desiccant for bottle packs.

Data regarding the bulk packaging have been provided and is acceptable.

3.1.3.4. Stability of the product

Stability study has been performed on three validation batches of 600 mg dosage strength. The samples were packed in the proposed market packs (HDPE bottles and OPA/Al/PVC//Al blister) and in bulk / transportation packs (LDPE bag), in accordance with current ICH/CHMP guidelines. Batches are tested according to the initially set specification and after 12 months according to the specification previously provided (see AR of D80). After 17th months testing according to the specification currently provided in section P.5.1. has been done. Used analytical procedures are as described in section P.5.2

For primary packaging, OPA/Al/PVC//Al blister and HDPE bottles (HDPE/STB with 180 tablets, HDPE/STB with 60 tablets and HDPE/SG with 60 tablets), results of stability study are provided up to 18th months for three batches of 600 mg at 25°C/60% RH. Stability is on-going for all batches. At 40°C/75% RH up to 6 months for 3 validation batches results are enclosed. Accelerated stability is finished.

The following parameters were tested: description, assay by HPLC, related substances by HPLC, dissolution by HPLC, water by Karl-Fischer and microbial quality (at the initial time point, at the 6-month time point and annually following long-term conditions as well as after 6 months at accelerated storage condition).

All results were within proposed limits. Water results were practically not changed during whole stability testing at both conditions and both types of primary packaging. For assay slight decrease during the storage (similar results for both storage conditions and both type of packaging) is noted.

Provided results of bulk stability study indicate that film-coated tablets of both strengths are stable for 12 months in bulk packaging. Transportation conditions are stated in section P.3.3.

The tablets packed in bottles have been tested for photostability as per ICH Q1B. A sample (HDPE bottle packs) protected from light, which ran in parallel to the directly exposed sample, was tested for use as a control. Based on the results it can be concluded that the drug product is photostable Photostability testing was not conducted with samples packed in blister, but it can be concluded that similar results can be expected for blisters (results for directly exposed tablets are in line with set requirements). This is acceptable.

Stability after opening has been investigated. The in-use stability study has been initiated on Raltegravir 600 mg film-coated tablets in compliance with the CPMP guidance CPMP/QWP/2934/99. The in-use stability study has been designed in phases for HDPE bottle pack. Sampling and testing methodology is enclosed.

3.1.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The drug substance raltegravir potassium is included in the current European Pharmacopoeia (04/2018:2887, corrected in version 10.3). The drug substance documentation is presented in the form of an Active Substance Master File / ASMF.

No Major Objection is raised on the quality of the active substance. Proposed drug substance specification is acceptable. Overall, several other concerns have been raised in connection with identified issues during review of the data.

The description and composition of the finished product are in general satisfactorily described.

Formulation development was based on the composition of the reference product Isentress 600 mg film-coated tablet.

One major objection is raised regarding the limit for dissolution. Several other concerns about the different section of the documentation also need to be clarified. The detailed information is given in the quality part of the assessment report.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Raltegravir Viatris 600 mg film-coated tablets cannot be recommended for approval, before satisfactory responses to the major quality concern and other concerns, as outlined in the List of Questions, are provided.

3.1.6. Recommendation(s) for future quality development

Not applicable.

3.2. Non clinical aspects

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

Non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate, since the applicant adequately discussed the impurity profile.

3.2.1. Ecotoxicity/environmental risk assessment

When default values and maximum daily dose of 1200 mg are used, the $PEC_{SURFACE\ WATER}$ for raltegravir is 6 µg/L, which is above the action limit of 0.01 µg/L.

The Applicant refined Fpen value based on annual consumption and European disease prevalence data. In both cases the $PEC_{surface\ water}$ was still above the action limit.

The Applicant submitted consumption data of raltegravir 400 mg and 600 mg film-coated tablets for 26 different member states for last 4 years (April-March 2017/2018, 2018/2019, 2019/2020, 2020/2021). Consumption of raltegravir in EU did not significantly increase in the last 4 years, so it can be assumed that introduction of Raltegravir Viatris to the market is unlikely to result in significant increase in the exposure of environment to the active substance.

3.2.2. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate, since an assessment of the impurities and degradants present in the drug substance and product is adequately discussed, along with what is known of their potential pharmacologic and toxicologic effects. The impurities which are above the qualification threshold have been adequately justified based on the toxicological data. Therefore, Module 2.4 is adequately updated with requested data, as well as Module 1.4.2 accordingly. New references are provided in the Module 4.3. The front page of the updated Overview is adequately dated.

Environmental risk assessment (ERA):

Even though the Applicant's approach in PEC surface water calculations and Fpen refinements is not supported, since consumption of raltegravir in EU did not significantly increase in last 4 years it is assumed that marketing authorisation of the proposed product will not lead to any increased environmental risk.

3.2.3. Conclusion on non-clinical aspects

Non-clinical part of the proposed SmPC is identical to the reference product.

Overview based on literature review is appropriate. Additional *in vitro* genotoxicity studies (Ames test and chromosome aberration test) and a repeat dose toxicity study have been conducted in order to assure there are no safety concerns with the test product.

As argument that the introduction of their product to the market will not lead to an increase of environmental exposure the Applicant provided consumption data of the raltegravir in kg/year over last 4 years in several involved Member States. In observed period, consumption of raltegravir in EU did not significantly increase.

3.3. Clinical aspects

The report, written in 2022, refers to 50 publications dating up to year 2021. The Clinical Overview on the clinical pharmacology, efficacy and safety of raltegravir is adequate.

The clinical parts of the proposed SmPC are in line to the SmPC of the originator product.

The proposed pack sizes correspond to the originator's pack sizes range and are considered acceptable.

3.3.1. Exemption

- **Tabular overview of clinical studies**

To support the application, the Applicant has submitted one bioequivalence study. The biowaiver was requested for Raltegravir Viatris 400 mg film-coated tablets. The requirements for biowaiver according to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr** were considered fulfilled (same manufacturing process, same qualitative composition and dose proportionality, linearity of raltegravir pharmacokinetics, as well as appropriate *in vitro* dissolution data).

The clinical development programme regarding biowaiver request for the 400 mg strength was in the accordance with the scientific advice given to the Applicant. However, background information on the

reference product presented for the purpose of scientific advice omitted the fact that tablets of 400 mg and 600 mg are significantly different in terms of *in vivo* pharmacokinetics.

Formulations of the 400 mg and the 600 mg of the reference product Isentress differ significantly which consequently impacts their pharmacokinetics (Isentress EPAR, Procedure No. EMEA/H/C/000860/X/0059). Therefore, the two formulations of the reference product are not interchangeable when it comes to the posology, since 3x400 mg is not bioequivalent to 2x600 mg (Isentress EPAR, Procedure No. EMEA/H/C/000860/X/0059). The stated is explicitly reflected in the posology recommendation for the reference product. Therefore, bioequivalence of the 600 mg test formulation with the respective reference formulation cannot be extrapolated to the 400 mg test formulation on the basis of dissolution profiles similarity between 600 mg and 400 mg strengths of the test product. Following D120 List of questions, the application for 400 mg strength was withdrawn.

3.3.2. Clinical pharmacology

3.3.2.1. Pharmacokinetics

Study RALT-TBZ-1003

Methods

- **Study design**

This was randomisation blinded, four-period, two-treatment, two-sequence, cross-over study investigating the bioequivalence of Raltegravir 600mg tablets of Viatris Limited with ISENTRESS® (raltegravir) tablets 600mg, Merck Sharp & Dohme, following a single oral dose administered in one hundred and eight (108) healthy adult human volunteers under fasting conditions.

Study plan and subjects' randomization:

It was planned to conduct the study with 108 subjects in a single group initially, however due to non-availability of sufficient number of eligible volunteers for the study on the particular day, the study was conducted in three groups.

Volunteers were divided into three groups, 32 subjects for group-I (subject numbers 01-32), 32 subjects for group-II (subject numbers 33-64) and 44 subjects for group-III (subject numbers 65-108). Each subject was administered a single oral 600 mg dose of either test or reference product in 4 periods. A minimum of 7 days wash-out period separated each dosing in the groups.

The randomisation scheme was computer generated by a statistician and the subjects were randomised prior to period-1 dose administration.

Drug intake procedures:

In each period, every subject had an overnight fast for at least 10.00 hours prior to dosing till at least 04.00 hours after the dosing. In each study period, a single oral dose of either test product or reference product was administered orally to the subjects in sitting posture with 240 ± 2 ml of water at ambient temperature on the day of dosing as per randomisation schedule under fasting conditions. Subjects were instructed not to chew or crush the drug product and were asked to swallow the drug.

During confinement study hours subjects were allowed water ad libitum. However, in general, water consumption was controlled. Water was given 1 hour before dosing and 1 hour after dosing, except 240 ± 2 ml of ambient temperature water given for administration of the dose, but was

allowed at all other times. Standard low-fat meals or snacks were served after check-in and at 4.00, 8.00, 12.00, 24.00, 28.00, 32.00, 36.00 hours after dosing (with a grace period of + 45 minutes) and before check-out of each study period. Subjects were generally remained seated, in an upright position for 2 hours following drug administration to ensure proper stomach emptying except for brief periods when subjects were permitted to leave their seats under close supervision. After 2 hours, subjects could have been engaged in normal activity.

Sampling schedule and sample processing:

During each study period, 27 PK blood samples (4 ml each) were collected in blood collection tubes containing K_3 EDTA, before dosing (0.00) and at the following times thereafter: 0.167, 0.33, 0.50, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours. The pre-dose blood draw was collected no earlier than 120 minutes prior to dosing. The total volume of blood collected per subject in this study was 480.8 ml. The actual time at which each blood sample was collected was recorded by clinical staff.

Blood samples collected from each subject through an indwelling cannula placed in a forearm vein were transferred into pre-labeled K_3EDTA vacutainers, used as an anticoagulant. Within 45 minutes, the collected blood samples were placed in a refrigerated centrifuge at 3000 rpm for 10 minutes and 4ºC ± 3ºC. After centrifugation plasma samples were separated and transferred into two different vials (Aliquot 1 of 2 and Aliquot 2 of 2).

All plasma samples were stored at a temperature of -70°C at the clinical site until transferred on dry ice to analytical site where they were kept at the same temperature. Transfer of the samples into the freezer takes place no later than 90 minutes after the start of centrifugation. The plasma samples of subjects were analysed using LC/MS/MS method for raltegravir over a concentration range of 25.035 to 15020.985 ng/ml.

- **Population studied**

A total of 108 male subjects (3 groups), aged 19-44 years, BMI 18.8 – 29.9 kg/m^2 were enrolled and dosed in the study. One subject discontinued and 107 of them completed the study and were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The analytical portion of the bioequivalence Study No. RALT-TBZ-1003 was conducted at the Bioanalytical Laboratory of the CRC-determining plasma Raltegravir concentrations in the clinical samples from the fasting Bioequivalence study.

The analytical method used in the study is mostly acceptable, since it is validated according to the Guideline on a bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2**. The method reproducibility was assured.

- **Pharmacokinetic Variables**

The following pharmacokinetic parameters were used as primary:

C_{max}: Maximum observed plasma concentration following each treatment.

AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.

- **Statistical methods**

This study was conducted in three groups and the group factors were considered in the ANOVA model i.e., group, sequence, treatment, subject (sequence*group), period (group), group*sequence and treatment*group and there were no 'treatment*group' factor interaction. Hence, the statistical analysis was carry-out without group factors i.e., sequence, treatment, subject (sequence), period in ANOVA for pharmacokinetic parameters C_{max} and AUC_{0-t} for Raltegravir.

For parameter C_{max} it was possible to widen the acceptance criteria based on high intra-subject variability calculated from data utilizing the two administrations of the reference product. If within reference variability was <30% then the normal BE limits i.e., 80.00 to 125.00 could be applied. The possibility to widen the acceptance criteria based on high intra-subject variability did not apply to AUC and the acceptance range remained at 80.00 – 125.00%.

Results

The results are summarised in Table 1 below. The test to reference ratio of geometric LS means and corresponding 90% confidence interval of the C_{max} and AUC_{0-t} were all within the bioequivalence acceptance range (Table 2).

T_{max} was not observed in any of the subjects in the first sample time point. Concentrations for both reference and test drug in pre-dose time point were BLQ. The LLOQ of 25.035 ng/mL was sensitive enough to detect levels of 5% of the minimum C_{max}. Residual area value was above 20% of AUC_{0-inf} only for subject 79 (test product, period 1).

Due to the CV% >30% for C_{max}, the acceptance range for its 90% confidence interval the Applicant has widened to 72.15% - 138.59%, which is the range corresponding to 45% coefficient of variation. According to the Guideline on bioequivalence, for the given CV value of 43.8%, the appropriate acceptance range should have been determined using the applicable formula: [U, L] = exp [±k·sWR]. Thus, the acceptance range for 90% confidence interval for the ratio of GLSM should have been widen to 72.73% - 137.49%. However, this non-compliance did not affected conclusion on the primary outcome of the study, since 90%CI of C_{max} are still within the specified limit.

Table 1 Pharmacokinetic parameters for raltegravir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ hr*ng/ml	19909.418	7036.7632	19209.672	7330.8245
$AUC_{(0-\infty)}$ hr*ng/ml	20353.736	7023.9346	19692.497	7294.8330
C_{max} ng/ml	8519.498	4055.3475	6894.231	3127.2802
T_{max}* hr	1.00	(0.33 – 4.50)*	1.25	(0.33 – 4.50)*
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2 Statistical analysis for raltegravir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
C_{max}	123.02%	**114.27% – 132.45%**	43.8%
$AUC_{(0-t)}$	104.51%	**99.31% – 110.00%**	32.0%

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
* estimated from the Residual Mean Squares			

Safety

There were no deaths or serious AEs reported during the conduct of the study. Tolerability of the test product was not significantly different from that for the reference product and thus, is acceptable.

3.3.2.2. Pharmacokinetic conclusion

Based on the presented bioequivalence study Raltegravir Viatris 600 mg film-coated tablets is considered bioequivalent with ISENTRESS® film-coated tablets 600mg, Merck Sharp & Dohme.

3.3.2.3. Pharmacodynamics

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

3.3.3. Discussion on clinical pharmacology

This application concerns a generic version of raltegravir film-coated tablets. The reference product Isentress is indicated for the treatment of human immunodeficiency virus (HIV-1) infection. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the Applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with a randomisation blinded, four-period, two-treatment, two-sequence, cross-over study. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. According to the SmPC of the reference product Isentress, no specific recommendation regarding food intake is given for raltegravir posology since it can be taken with or without food. Therefore, the conduct of the single dose study under fasting conditions as most sensitive conditions to detect a potential *in vivo* difference between formulations is considered adequate. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Raltegravir Viatris 600 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Isentress 600 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and $AUC_{0-\infty}$ were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Due to the CV% >30% for C_{max}, the acceptance range for its 90% confidence interval has been widened to 72.73% - 137.49%. Bioequivalence of the two 600 mg formulations was demonstrated in study RALT-TBZ-1003.

Before performing study RALT-TBZ-1003 the applicant performed another BE study (RALT-1-19208), intended to be pivotal, where BE was not demonstrated for C_{max} as the confidence interval was outside the maximally widened acceptance criteria and the point estimate was outside the conventional acceptance criteria (80-125%): T/R % 134.66 (90% CI 121.97 - 148.68). According to the BE guideline, the body of evidence must be considered as a whole and the existence of a study which

demonstrates bioequivalence does not mean that those which do not can be ignored. The Applicant interprets the failure of the RALT-1-19208 study to demonstrate BE with the inadequate sample size which was calculated based on the assumptions of intra-subject CV of 50% and a T/R% of 115% (observed intra-subject CV was lower ~42% and T/R% was higher ~123%). While the suboptimal sample size may have accounted for the failure, it should be noted that 90% CI for Cmax was likewise not exceptionally wide and was almost completely outside the upper boundary of conventional acceptance 80-125%. The data pooling of the two studies results have been provided. Again, in the pooled analysis, the point estimate was outside the 80-125% criteria: T/R % 127.1% (90% CI 119.83 – 134.82). It is noted that first study was intended to serve as a pivotal study and the applicant did not plan to apply two-stage design, therefore the analysis provided is done post-hoc. However, the pooled estimates of the primary parameters were not estimated correctly. The applicant is asked to repeat the analysis with corrected subject identifier, using the analysis without the study*treatment interaction. Since adjusting probability is not possible, the applicant is asked to provide tipping point analysis, providing the largest possible coverage probability of the confidence interval to be in the widened acceptance range. Also, the applicant should thoroughly discuss the bioequivalence assumption made after failing to demonstrate the bioequivalence in the study RALT-1-19208 in terms of raising the number of subjects, which would actually lead to a higher possibility of entering the acceptance criteria. **(MO)**

In conclusion, the justification for the claim that bioequivalence has been demonstrated is not considered adequate.

A list of questions is proposed for the MWP regarding several methodological aspects (please see section 1.1 of this AR).

3.3.4. Clinical efficacy

No new studies were submitted, and none are required for generic applications.

3.3.5. Clinical safety

No new studies were submitted, and none are required for generic applications.

3.3.6. Post marketing experience

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

3.4. Discussion on clinical aspects

3.5. Conclusions on clinical aspects

Based on the presented bioequivalence study (RALT-TBZ-1003) Raltegravir Viatris 600 mg film-coated tablets was found bioequivalent with ISENTRESS® film-coated tablets 600mg, Merck Sharp & Dohme. However, the first study (RALT-1-19208) intended to be pivotal, failed to show bioequivalence. A justification for the claim that bioequivalence has been demonstrated is however not considered adequate and data analysis should be repeated since the pooled estimates of primary parameters are not estimated correctly. **(MO)**

All "other" issues were resolved.

3.6. Risk management plan

The Applicant has submitted a risk management plan (RMP) (version 0.1) in support of its application under Article 10(1) of Directive 2001/83/EC through centralized procedure.

The Applicant should bear in mind that a new version number and a date need to be assigned each time the RMP is updated and submitted for assessment.

Part I Overview

The Applicant has presented Part I as described in the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (EMA/PRAC/613102/2015 Rev.2). However, information on dosage should summarise information on dosing only; therefore, information on method of administration should be removed from the Part I of the RMP. (D120 LoQ)

The Applicant provided updated RMP (version 0.2) in which Part I Overview is updated as requested.

3.6.1. Safety Specification

Summary of safety concerns

The Applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety of 1200 mg once daily (QD) (2x600mg tablets) dosing in pregnant women

3.6.1.1. Discussion of the safety specification

The Applicant aligned the summary of safety concerns with the one publicly available on the EMA website (RMP summary of the reference medicinal product Isentress, last updated on 17 August 2021).

3.6.1.2. Conclusions on the safety specification

Having considered the data in the safety specification

The rapporteur agrees that the safety concerns listed by the applicant are appropriate.

3.6.2. Pharmacovigilance Plan

3.6.2.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are considered necessary.

3.6.2.2. Summary of additional PhV activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Table 5: Part III.2- On-going and planned additional pharmacovigilance activities

Study & Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required Additional Pharmacovigilance Activities				
Antiretroviral Pregnancy Registry On-going	To collect information on the risk of birth defects in patients exposed to Raltegravir during pregnancy	Missing information: "Safety of 1200 mg once daily (QD) (2x600mg tablets) dosing in pregnant women"	Semi-annual reports	Semi-annual reports
			Final Report	When 1000 first trimester exposures to each antiretroviral therapy is attained or when a subsequent mechanism for monitoring pregnancy outcomes emerges (e.g., standardized national monitoring program).

Study title

The Antiretroviral Pregnancy Registry

Rationale and study objectives

The purpose of the Antiretroviral Pregnancy Registry is to detect major teratogenic effects of any of the Registry drugs when administered to pregnant women. The combination of increased numbers of HIV-infected pregnant women and the lack of foetal safety data concerning these drugs used during pregnancy, make such a registry an essential component of the ongoing program of epidemiologic studies of the safety of these medications.

The objectives of the Antiretroviral Pregnancy Registry are as follows:

- To prospectively collect data concerning
    1. exposure to the Registry drugs during pregnancy,
    2. potential confounding factors, and
    3. outcome of pregnancy
- To review reported cases of possible birth defects
- To estimate the risk of birth defects occurring in live-born offspring of women exposed to antiretroviral medications followed in the Registry during pregnancy
- To detect any increase in the prevalence or pattern of birth defects among pregnancies exposed to antiretroviral medications followed in this Registry

Study design

This is a prospective, observational, exposure-registration, and follow-up study of pregnant patients exposed to antiretroviral drugs. Health care providers voluntarily report exposures to Registry drugs. To assure participant confidentiality, no direct patient identifiers are collected. The intent of the Registry is to collect data on exposures to Registry drugs used alone or in combination, along with potential confounding factors (such as maternal age, clinical category, disease severity), and

information related to the outcome of the pregnancy. The Registry encourages enrolment as early in the pregnancy as possible, before any prenatal testing results are known.

3.6.2.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.6.3. Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

3.6.4. Risk minimisation measures

3.6.4.1. Summary of additional risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety of 1200 mg once daily (QD) (2x600mg tablets) dosing in pregnant women	Routine risk minimisation measures Routine risk communication: *SmPC section 4.6* *PL section 2* Other risk minimisation measures beyond the Product Information: Medicine's legal status: *Restricted medical prescription*	Routine pharmacovigilance activities Additional pharmacovigilance activities: *Antiretroviral Pregnancy Registry*

3.6.4.2. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.6.5. Summary of the risk management plan

The public summary of the RMP does not require revision.

3.6.6. PRAC Outcome

PRAC agrees with the assessment of the RMP V 0.2

3.6.7. Conclusion on the RMP

The PRAC Rapporteur considered that the risk management plan version 0.2 is acceptable provided that the applicant adds the APR in the annex 2 of the RMP as part of the PV study program.

3.7. Pharmacovigilance

3.7.1. Pharmacovigilance system

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

3.7.2. 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.

4. Benefit risk assessment

This application concerns a generic version of Raltegravir tablets. The reference product Isentress is indicated for *the treatment of human immunodeficiency virus (HIV-1) infection in adults, and paediatric patients weighing at least 40 kg in combination with other anti-retroviral medicinal products*.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a blinded, four-period, two-treatment, two-sequence, cross-over study. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Raltegravir did not meet all protocol-defined criteria for bioequivalence when compared with the Isentress. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} were contained within the protocol-defined acceptance range of 80.00 to 125.00%, however for C_{max} parameter the acceptance range was widened to 72.15% - 138.59%, due to the CV% >30%. Bioequivalence of the two formulations was demonstrated, however pooled estimates of the parameters considering the first study RALT-1-19208 were not estimated correctly, due to an oversight in the raw data. Also, the applicant has not provided thorough justification for bioequivalence claim.

A benefit/risk ratio comparable to the reference product can therefore not be concluded.

The application contains inadequate clinical data. The aspects that are inadequately demonstrated are outlined in the List of outstanding issues.

4.1. Conclusions

The overall benefit/risk balance of Raltegravir Viatris is negative.