10 November 2016
EMA/851324/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darunavir Mylan

International non-proprietary name: darunavir

Procedure No. EMEA/H/C/004068/0000

Note

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

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List of abbreviations

% CV	% Coefficient of Variation
3TC	Lamivudine
AACTG	Adult AIDS Clinical Trial Group
AAG	Albumin and α1-acid glycoprotein
AAS	Atomic Absorption Spectrometry
ABC	Abacavir
ADRs	Adverse drug reactions
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
AMPK	5' AMP-activated protein kinase
ANOVA	Analysis of Variance
APV	Amprenavir
ARC	AIDS-related complex
ART	Antiretroviral therapy
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical classification
ATV	Atazanavir
AUC	Area Under Curve
AUC0-∞	The Area Under the Plasma Concentration Versus Time CurveFrom Time Zero to Infinity
AUC0-t	The Area Under the Plasma Concentration Versus Time Curve From Time Zero to the Last Measurable Concentration
AZT	Azidothymidine/Zidovudine
bid	Twice daily
BMI	Body mass index
BP	Blood Plasma
cART	Combination antiretroviral therapy
CD	Circular dichroism
CD4	Cluster Of Differentiation 4
CHMP	Committee for Medicinal Products for Human use
CL/F	Fractional clearance
CLCR	Creatinine clearance
CLD	Chronic liver disease
CSF	Cerebrospinal fluid
CYP	Cytochrome
desRFB	desacetylrifabutin
ddATP	dideoxyadenosine-5′-triphosphate
ddCTP	2',3'-dideoxycytidine 5'-triphosphate
DRV	Darunavir
DRV/r	Darunavir/ritonavir
EC	European Commission
EU	Europe
FDC	Fixed Drug combination
FPV	Fosamprenavir
FTC	Emtricitabine
GC	Gas Chromatography
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
HAART	Highly Affective Antiretroviral Therapy
HIV	Human immunodeficiency virus
HM-HDPE	High Molecular Weight High Density Polyethylene
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
hr	Hour
HR	Hazard ratio
HS	hypersusceptibility
IAS-USA	The International AIDS Society-USA

IC	Intracellular
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQ	Inhibitory quotient
IR	Infrared
IN	integrase
i.v.	intravenous
ITT	Intent to treat
KF	Karl Fischer titration
L/hr	Litres per hour
LAM	Lamivudine
LDPE	Low Density Polyethylene
LOD	Limit of detection
LOD	Loss on drying
LSM	Least Square Mean
MDR	Multi drug resistant
NA	Nucleoside analogues
NARTI	Nucleoside analogue reverse transcriptase inhibitors
NFV	Nelfinavir
ng/ml	Nano gram per millilitre
NMR	Nuclear Magnetic Resonance
NNRTI	Non nucleside reverse transcriptase inhibitors
NONMEM	Nonlinear mixed-effect modelling
NRTI	Nucleside reverse transcriptase inhibitors
NVP	Nevirapine
OPA	Oriented polyamide film
P-gp	P-glycoprotein
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PI	Protease Inhibitor
PK	Pharmacokinetic
PNP	Purine nucleoside phosphorylase
PP	Polypropylene
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QD	Quarter in die
RFB	rifabutin
RH	Relative Humidity
RNA	Riboxy nucleic acid
RR	Relative risk
RT	Reverse transcriptase
RTI	Reverse transcriptase inhibitors
RTV	Ritonavir
SD	Standard deviation
SmPC	Summaries of product characteristics
SOR	Specific optical rotation
T/R	Ratio Of Test and Reference
t1/2	The elimination half-life
TDM	Therapeutic Drug Monitoring
tmax	Time of the maximum measured plasma concentration
QOD	Once daily
UV	Ultraviolet
Vd	Volume of distribution
WHO	World Health Organisation
XR(P)D	X-Ray (Powder) Diffraction
µM	Micro meters

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 31 July 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Darunavir Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014

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

The applicant applied for the following indication:

Darunavir, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir Mylan 75 mg, 150mg, 300mg, 600mg tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in ART-experienced paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with darunavir co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of Darunavir Mylan.

Darunavir Mylan 400mg and 800mg tablets, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).

Darunavir Mylan 400mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 12 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).
- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir (see sections 4.2, 4.3, 4.4 and 5.1).

The legal basis for this application refers to:

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

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

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Prezista 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 12 February 2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/380/001-005 and 007-008

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

- Product name, strength, pharmaceutical form Prezista 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 12 February 2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/380/001-005 and 007-008

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

- Product name, strength, pharmaceutical form: Prezista 600 mg, film-coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 12 February 2007
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/06/380/002
- Bioavailability study number(s): BA14101915-01

- Product name, strength, pharmaceutical form: Prezista 800 mg, film-coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 12 February 2007
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/06/380/007
- Bioavailability study number(s): BA14101343-01

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 31 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 November 2015.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection was conducted at one clinical facility and at the sponsor site, both located in India between the 3rd to the 7th of November 2015. The outcome of the inspection carried out was issued on 14 December 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 December 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 May 2016.
- During the PRAC meeting on 13 May 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 May 2016, the CHMP agreed on a list of outstanding issues to be

addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 1 august 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issued to all CHMP members on 26 August 2016.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issues on 12 October 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issued to all CHMP members on 26 October 2016.
- During the meeting on 10 November 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Darunavir Mylan.

2. Scientific discussion

2.1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumours. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, pre-seminal fluid, and breast milk. This transmission can involve anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above bodily fluids. During replication in the HIV life-cycle, gag and gag-pol gene products are produced as precursor polyproteins which are subsequently processed by a virally encoded protease to provide structural proteins (p17, p24, p9 and p7) and essential viral enzymes, including protease (PR), reverse transcriptase (RT) and integrase (IN). All three retroviral enzymes have been identified as potential drug targets. Specifically, the critical function of HIV protease has made it an important target for the treatment of HIV/AIDS.

Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART. This has been highly beneficial to many HIV-infected individuals since its introduction in 1996 when the protease inhibitor-based HAART initially became available. Current optimal HAART options consist of combinations (or "cocktails") consisting of at least three drugs belonging to at least two types, or "classes," of antiretroviral agents. Currently typical regimens consist of two nucleoside analogue reverse transcriptase inhibitors plus either a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI). Since the advent of the first PI, saquinavir, a number of PIs have been introduced in the regimens of highly active antiretroviral therapy or HAART. Thus improved HAART regimens have shown reduced viral load, increased CD4+ T-cell counts and drastically lowered AIDS related deaths in the US and industrialized nations. Standard goals of HAART include improvement in the patient's quality of life, reduction in

complications, and reduction of HIV viremia below the limit of detection, but it does not cure the patient of HIV nor does it prevent the return, once treatment is stopped, of high blood levels of HIV, often HAART resistant. For some patients, which can be more than fifty percent of patients, HAART achieves far less than optimal results, due to medication intolerance/side effects, prior ineffective antiretroviral therapy and infection with a drug-resistant strain of HIV. Non-adherence and non-persistence with therapy are the major reasons why some people do not benefit from HAART. The reasons for non-adherence and non-persistence are varied. Major psychosocial issues include poor access to medical care, inadequate social supports, psychiatric disease and drug abuse. HAART regimens can also be complex and thus hard to follow, with large numbers of pills taken frequently. Side effects can also deter people from persisting with HAART; these include, dyslipidaemia, diarrhoea, insulin resistance, an increase in cardiovascular risks and birth defects. Anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS.

As the number of agents that are used to treat HIV increases, the decisions regarding which antiretroviral agents to select in each clinical setting become more complex. The choice of the components of the regimen for patients who have an extensive treatment history relies on a careful assessment of (1) that past treatment history, (2) the response to prior agents, and (3) the results of past and current resistance tests (Haubrich R., 2007).

Darunavir is a second-generation PI that has been initially approved in treatment-experienced and -naive patients with a *00 mg q.d posology in combination with 100 mg of ritonavir. At the dose of 600 mg combined with 100-mg ritonavir b.i.d., it has demonstrated substantial virologic and immunologic responses in treatment-experienced patients with advanced HIV-1 disease, and the responses were greater than those seen in the control PI/ritonavir arm. In addition, darunavir/ritonavir added as a full active drug with two active drugs raltegravir and etravirine in heavily previously treated patients from the TRIO study has shown high rates of viral suppression. Furthermore, the rates of virologic suppression were comparable to those expected in treatment-naive patients (Phung BC *et al*., 2011). Darunavir when used without ritonavir have inadequate bioavailability and should never be used as unboosted PIs (Boyd SD *et al*., 2011).

Darunavir is an HIV protease inhibitor for use in combination therapy of HIV infection in previously treated adults. Darunavir has the advantage of retaining virological activity in the presence of multiple protease mutations. It is coadministered with low-dose ritonavir, which increases its bioavailability. It should also be taken with food to increase its absorption. Adverse effects are comparable with other protease inhibitors and include diarrhea, nausea, headache, and increased aminotransferase activity and serum lipid concentrations. Since darunavir is an inhibitor and substrate of CYP3A, it can increase serum concentrations of other drugs metabolized by this enzyme and its own metabolism may be affected by inducers or inhibitors of it (Eric Scholar., 2009).

This application is for a generic form of darunavir in strength of 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg. This is an abridged application submitted under Article 10.1 of Directive 2001/83/EC. An abridged application is appropriate since the product in this application is essentially similar to the existing licensed product namely ‘PREZISTA’ (darunavir ethanolate) film-coated Tablets. The active ingredient and the route of administration are the same for both products. In addition, the proposed SPC for the applicant’s Darunavir has been based on the ‘PREZISTA’ (darunavir ethanolate) film coated Tablets.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 75 mg, 150 mg, 300 mg, 400 mg, 600 mg, 800 mg of darunavir as active substance.

Other ingredients in the presentations are:

Tablet core: silica colloidal anhydrous, cellulose microcrystalline, crospovidone, sodium starch glycolate, hypromellose, magnesium stearate.

Tablet Film-coating: polyvinyl alcohol partially hydrolysed, titanium dioxide, macrogol, talc.

The product is available in cold form PVC/Al/OPA-Al blister, PVC/PE/PVDC-Al blister and HDPE bottle with PP screw cap as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of darunavir is (1S, 2R)-3-[[(4-amino-phenyl)sulfonyl](2-methylpropyl)amino-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R, 3aS, 6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester corresponding to the molecular formula $C_{27}H_{37}N_3O_7S$. It has a relative molecular mass of 547.66 g/mol and the following structure:

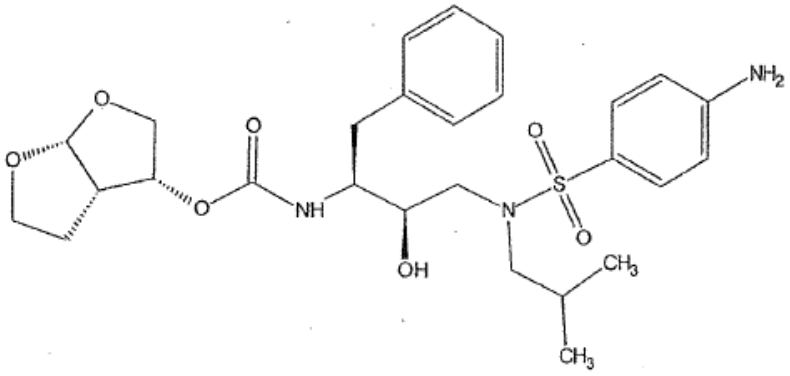

Figure 1. Structure of Darunavir

Darunavir is a white to light brown colour slightly hygroscopic powder, very slightly soluble in aqueous solutions, freely soluble in acetone, sparklingly soluble in ethyl acetate.

Darunavir exhibits stereoisomerism due to the presence of five chiral centres. One chiral centre originates in a starting material, whilst the others are generated during the process. The synthetic strategy and process design such as the starting material and reagent selection, process parameters, and in-process controls

ensure the desired configuration at each of the five chiral centres. The darunavir enantiomer (also called isomer 7) and the isomers 8-15 are combinations of two isomers of synthesis intermediates (DRV-II and DRV-IIA). It was considered unlikely that these isomers are formed. Hence they are not controlled in the final active substance. The isomers 1-5 are monitored routinely in active substance specifications. The isomer-6 content was below the detection limit in three darunavir production scale batches. Therefore, its control is not included in the active substance specification.

Polymorphism has been observed for darunavir. The literature states that darunavir exists as ethanolate, hydrate and amorphous forms. The amorphous form is consistently produced by the active substance manufacturer. Amorphous form control has been included in the active substance specification.

Manufacture, characterisation and process controls

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

A single source of active substance is used although in total three manufacturers are used, responsible for different steps.

Darunavir is synthesised in 3 main parts each of them involving several steps. Two well defined starting materials with acceptable specifications are used in the synthesis. One originally-proposed starting material was re-defined during the procedure at the request of CHMP to ensure that enough of the process is conducted under GMP.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Darunavir is characterized by IR, UV, NMR, mass spectroscopy, elemental analysis, and XRD. Further data were provided to confirm the absolute configuration of darunavir active substance and its enantiomeric purity. Darunavir is amorphous in nature and the development of single crystals is not possible. Hence crystallographic studies were attempted on the darunavir crystalline which is n-1 stage for darunavir amorphous. However no suitable crystals were obtained, hence crystallographic studies were performed on darunavir ethanolate which were grown from ethanol by slow evaporation method. The obtained single crystal XRD data confirmed the stereochemistry of darunavir at chiral centres is C(3)-R, C(3A)-S, C(6A)-R, C(11)-S and C(19)-R. The ASMF holder also identified the absolute stereochemistry of a darunavir enantiomer using the circular dichroism (CD) technique. Specific optical rotation (SOR) data of darunavir enantiomer, darunavir amorphous in-house working standard and three darunavir validation batches were compared. The CD analysis and SOR data confirmed the absolute configuration of darunavir enantiomer as dextrorotatory i.e (S) or (+) and darunavir amorphous as levorotatory i.e (R) or (-).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is first packed in translucent LDPE bag, securely folded and twist-tied with a plastic rope. The LDPE bag complies with the EC Regulation 1282/2011. The latter is placed in another translucent polyethylene bag (HMLDPE), which is flushed with nitrogen. It is surrounded by silica gel and molecular

sieves, and then heat sealed. The translucent polyethylene bag (HMLDPE) is placed in a triple laminated aluminium bag, flushed with nitrogen, surrounded by silica gel and molecular sieves, and then heat sealed. The triple laminated bag is put into HDPE drum.

Specification

The active substance specification includes tests for appearance, solubility, identification (HPLC, IR), water content (KF), heavy metals (Ph.Eur.), sulfated ash (Ph.Eur.), related substances (HPLC), assay (HPLC), chiral purity (HPLC), residual solvents (GC), palladium content (AAS), polymorph identification (PXRD) and particle size (laser diffraction).

The analytical procedures used by the finished product manufacturer to test the active substance are identical to those of the active substance manufacturer. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis for four production scale batches and two pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on three production scale batches of active substance from the proposed supplier stored in the intended commercial packaging for 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 parameters description, identification by IR, HPLC and XRD, water content, related substances, assay, and chiral purity have been investigated. The analytical methods used were the same as for release and were demonstrated to be stability indicating by forced degradation studies.

During long-term and accelerated conditions no significant changes have been observed. All results were within specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period of 36 months when stored in the proposed container below 30°C under nitrogen atmosphere as proposed by the ASMF holder. However the applicant follows a retest period shorter than the one proposed by the ASMF holder for the active substance.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product comes as white to off-white, oval shaped, biconvex film-coated tablets available in six strengths; 75 mg, 150 mg, 300 mg, 400 mg, 600 mg, 800 mg.

The aim was to develop a stable and robust formulation, bioequivalent to the reference product Prezista. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards

with the exception of the film coating opadry II, although it is composed of a mixture of compendial components. 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 formulation of the proposed product differs from the reference medicinal product in the active substance form. In the reference product the solvate form (ie darunavir (as ethanolate) is used whereas in the proposed finished product the amorphous form is used. The reference product does not contain the binder hypromellose (except in the 800mg strength) nor the disintegrant sodium starch glycollate but does contain sunset yellow FCF for the 400mg and 600mg strengths. The compatibility of the active substance with the excipients used in the proposed finished product has been adequately demonstrated. The roles, the choice of the excipients and their concentrations have been satisfactorily justified. The formulation used during clinical studies is the same as that intended for marketing.

The finished product is also for paediatric use, for paediatric patients from the age of 3 years and at least 15 kg body weight. Tablets dimensions are similar to the ones of the reference product. As it is the case for the reference product, the proposed 800 mg tablet is of the same size as the 600mg tablet in order not to be too large to be swallowed.

The 75 mg, 150 mg, 300 mg, 400 mg and 600 mg tablet strengths are fully dose/weight proportional. The 800mg tablet strengths is not dose/weight proportional with the other strengths.

The similarity of the developed product with the reference product was assessed by comparison of dissolution and impurity profiles and by bioequivalence (BE) studies.

Two bioequivalence studies were performed with the 600 mg and 800mg strengths showing bioequivalence between the proposed finished product and the reference medicinal product.

A bio-waiver was requested for the other strengths based on the result from BE-study with 600 mg strength. All the conditions for bio-waiver for additional product strengths as stated in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. Comparative dissolution profile was performed. Initially, the applicant submitted comparative dissolution profiles obtained with a dissolution method using a surfactant and a rotation speed of 75 rpm instead of 50 rpm. Following CHMP request to provide dissolution data in accordance with the Guideline on Bioequivalence, new dissolution data were provided at pH 3.0, 4.5 and 6.8 without the use of surfactant but using a 75 rpm rotation speed. CHMP requested dissolution data at pH 1.2 instead of pH 3.0 and a justification for the use of a rotation speed of 75 rpm instead of 50 rpm in line with the Guideline on Bioequivalence requirements. The applicant submitted comparative dissolution profiles at pH 1.2 and justified the use of the 75 rpm rotation speed by the fact that incomplete active substance release was observed at 50 rpm paddle agitation speed. The CHMP considered that incomplete drug release was not a justification to use a higher rotation speed, as it is not a criterion which may hamper comparability evaluation in dissolution. As the use of a higher rotation speed may result in a lower discriminatory power at the tested pH conditions, the applicant was requested to submit new dissolution data in pH 1.2, pH 4.5, pH 6.8 using a paddle speed of 50 rpm. The data provided showed similarity of the dissolution profiles at pH 1.2 but a lack of similarity between the bio-batch strength and the 75 mg, 150 mg and 300 mg strengths in pH 4.5 and pH 6.8 buffers. The lack of similarity at in pH 4.5 and pH 6.8 was justified by the very poor solubility of the active substance which leads to poor sink conditions. For the 600mg strength of the finished product lower active substance release was observed compared to the other strengths of the finished product. Due to the poor sink conditions the applicant performed comparative dissolution testing at “same dose” in pH 4.5 and pH 6.8 buffers using a rotation speed of 50rpm. The similarity factor was greater than 50 for the “same dose” dissolution study. Therefore the dissolution profiles of all these batches were considered similar. Dissolution studies between the bio-batch strength and the

additional strengths at 50rpm with surfactant also demonstrated similar profiles since more than 85% is dissolved within 15 minutes or f2 similarity factor was more than 50. Based on the dissolution data provided the applicant's request for a bio-waiver for the 75 mg, 150 mg, 300 mg and 400 mg strengths of the test product was considered acceptable.

The development of the dissolution method is described and the discriminatory power has been demonstrated. It is also considered that the applicant has adequately justified the choice of agitation speed and concentration of surfactant used in the dissolution method.

The impurity profiles of both generic and reference products in all strengths are similar.

Data demonstrating polymorphic stability during finished product manufacture and storage were provided and considered satisfactory.

The primary packaging is cold form PVC/Al/OPA-Al blisters, PVC/PE/PVDC-Al blisters and HDPE bottles with a PP screw cap. The material complies with Ph.Eur. and EC requirements. 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 nine main steps: sifting, granulation, drying, dry screening, sifting of extra granular materials, blending, compression, coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three pilot scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Process validation will be performed post-approval on the first three consecutive production scale batches of each strength. An acceptable validation plan has been provided.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), colour identification (titanium dioxide test), dissolution (UV), uniformity of dosage units (mass variation, Ph. Eur.), related substances (HPLC), assay (HPLC), water (KF) and microbiological test (Ph. Eur).

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 were provided for 3 pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 3 pilot scale batches of each strength of finished product stored according to the ICH guidelines:

- under long term conditions for up to 12 months for blister and 24 months for HDPE bottle at 25 ºC / 60% RH (all strengths except 800 mg)

- under long term conditions for up to 18 months at 25 ºC / 60% RH, under intermediate conditions for 12 months at 30 ºC / 75% RH (800mg tablet only, all packaging,)

- under accelerated conditions for up to 6 months at 40 ºC / 75% RH (all strengths, all packaging) .

The batches used are identical to those proposed for marketing and were packed in the three primary packaging proposed for marketing.

In addition, batches packaged in PVC/PE/PVdC blister and 100's HDPE bottle were exposed to light as defined in the ICH Guideline on Photostability Testing of New active Substances and Products.

In-use stability studies were performed on two batches of the 800 mg strength packaged in 90's HDPE bottle pack. In-use stability studies were also performed on two batches of two extreme strengths ie 75 mg and 600mg packaged in 100's HDPE bottle. In-line with CPMP guidance – Note for Guidance on In-use stability testing of human medicinal products - CPMP/QWP/2934/99, justification has been provided that the in-use stability of the 75 mg and 600 mg film-coated tablets can be extended to other middle strengths (ie darunavir 150 mg, 300 mg and 400 mg film-coated tablets) and that the containers size used to conduct the studies represents the worst case scenario in terms of head space to fill volume ratio. The sampling and methodology of the in-use studies were described and considered acceptable.

Stability samples were tested for description, assay, dissolution, related substances, water, and microbiological quality. The analytical methods used were the same as for release and were stability indicating.

All stability results are within specification limits and no specific trends are observed.

Photostability results showed that the finished product is not photosensitive.

The stability of the finished product in bulk shipment packs was assessed on three pilot batches of each strength at ICH accelerated i.e. 40 ± 2°C / 75 ± 5% RH and ICH long term i.e. 25 ± 2°C / 60 ± 5% RH stability conditions. The results support a 12 months holding time for the finished product in bulk shipment packs.

Based on available stability data, the proposed shelf-life of 24 months with no special storage precaution for all the presentations except the 800 mg strength in the PVC/PE/PVDC-Al blister that need to be stored below 25°C and the proposed in-use shelf-life (100 days for the 75/150/300/400/600 mg tablets – 90 days for the 800 mg tablet) as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

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 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.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (K_D of 4.5 x 10^{-12}M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

2.3.2. Pharmacokinetics

The pharmacokinetic properties of darunavir, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy

subjects may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

2.3.3. Toxicology

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone, nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in

rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

2.3.4. Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted. This was justified by the applicant as the introduction of Darunavir manufactured by Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all darunavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.5. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The impurity profile of the medicinal product being applied for has been adequately discussed.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.6. Conclusion on the non-clinical aspects

There are no objections to approval of Darunavir Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing darunavir. To support the marketing authorisation application the applicant conducted two bioequivalence studies with two-treatment, two-sequence, two-period crossover design under fed conditions. These were the pivotal studies for the assessment.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

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

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

Exemption

Biowaiver justification for Darunavir 75 mg, 150 mg, 300 mg and 400 mg film-coated tablets:

The bio-equivalence study was performed on Darunavir 600 mg film-coated tablets and the applicant requests that this study be extended to the lower strengths via bio waiver.

The applicant states that since all the requirements to waive bioequivalence studies for additional strengths as mentioned in CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 – January 2010 are fulfilled, the bioequivalence study results of Darunavir 600 mg film-coated tablets can be extended to Darunavir 75 mg, 150 mg, 300 mg and 400 mg film-coated tablets.

Linear pharmacokinetics of Darunavir

In adults, linear pharmacokinetics is observed after single dose administration over the 300 – 1200 mg darunavir dose range with 100 mg ritonavir. A biowaiver was considered acceptable, as for the 75 and 150 mg tablet formulations dissolution studies comparing the tablets with the 300 and 600 mg tablets showed comparable results.

Moreover, the tablets are dose-proportional, and darunavir with ritonavir shows linear pharmacokinetics after single dose administration (Assessment Report. EMEA. Prezista. 2009).

Also WHO prequalification document states that due to the linear / dose-proportional pharmacokinetics of danuravir and its low solubility, the maximum strength in the application to PQ (*i.e.*, 800 mg for the 400 mg, 600 mg and 800 mg strengths) can be employed in the bioequivalence study (Darunavir. WHO Guidance, 2014).

Also when darunavir was administered in combination with ritonavir, a potent inhibitor of CYP3A, the plasma concentration of darunavir was increased (Ruela Corrêa JC *et al*., 2012).

The requirements for the request of biowaiver for the following strengths: 75 mg, 150 mg, 300 mg and 400 mg film-coated tablets are considered fulfilled in line with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98- Rev 01.

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies (see below: section 2.4.2).

2.4.2. Pharmacokinetics

Study BA14101343-01 – Study Title:

Single dose oral bioequivalence study of Darunavir film-coated Tablets 800 mg and 'PREZISTA' (Darunavir Ethanolate) film-coated Tablets 800 mg with co-administration of 'NORVIR' (Ritonavir) film-coated Tablets 100 mg in healthy adult human subjects under fed conditions

Methods

This was a randomised, open-label, two-period, two-treatment, two-sequence, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Darunavir 800 mg film coated tablets (test manufactured by Mylan Laboratories India) and Prezista 800 mg film coated tablets (MAH: Janssen-Cilag International NV, Belgium and manufactured by Janssen-Cilag SpA, Italy) with co-administration of Norvir (ritonavir 100mg film coated tablets, MAH: AbbVie Ltd, UK and manufactured by Abbvie Deutschland GmbH) in 44 healthy, adult human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

Study design

Based on the randomised schedule and following an overnight fast of at least 8 hours in both periods each volunteer was served with a standardised breakfast on day 1, 2, 4 and 5 at about 30 minutes prior to dosing. A single oral dose of concomitant ritonavir medication was administered to the subjects twice daily at an interval of 12 hours from Day 1 to Day 5 and a single 800mg oral dose of investigational product (test or reference) was administered to the subjects on day 3. Administration of the morning concomitant medication and investigational product was done simultaneously on day 3 of each period.

Subjects were dosed while in sitting posture with 240ml of ambient temperature water. During confinement (Day 1 to 5), a standard meal was served at least 04 hours after dosing of IP/dosing of morning concomitant medication. Drinking water was not permitted one hour before dosing on day 3 of each period (dosing of investigational product) and until one hour post dose. Further meals/snacks after 04 hours post dose of IP/dosing of morning concomitant medication were served at appropriate times. Meals/snacks/breakfasts of identical composition and similar quantities were provided at approximately same times in all the periods.

The two periods were separated by a wash-out phase of at least 8 days.

Blood samples were taken at the following time points: pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 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, 48.00 and 72.00 hours after dosing. Blood sampling time adjustments are presented in the dossier.

After collection, the blood samples were placed in an ice bath until centrifugation and then placed in a refrigerated centrifuge within 30 minutes of blood sample collection, and then spun at 3000 rpm at 4°C for 15 minutes. The plasma was separated, transferred to labelled primary and secondary aliquots; primary aliquot was contained 1.5 ml of plasma and remaining amount was transferred in to secondary aliquot and stored in a freezer at – 70°C ±20°C at the clinical facility until shipment to analytical facility.

Test and Reference Products

Darunavir Mylan 800 mg Film-coated Tablets manufactured by Mylan Laboratories Ltd. (batch No 364428D; Exp. date, June 2016) has been compared to PREZISTA Film Coated Tablets 800 mg manufactured by Janssen-Cilag (Batch No: DLZ0Z00; Exp. Date, Sep 2015).

Population studied

47 healthy adult male human subjects were enrolled as per the protocol to ensure dosing of 44 subjects. Only 42 subjects were dosed and 37 completed the study. The dropouts are discussed below and as per the study protocol, the samples from Subject No.: 04, 23, 24, 31 & 32 were analyzed for Safety Evaluation, but the concentrations obtained were not considered for Pharmacokinetic and Statistical Evaluation.

Main inclusion criteria:

Healthy adult, non-smokers & non-tobacco using volunteers, 18 to 45 years old (both inclusive) with a Body Mass Index (BMI) 18.5 to 30.0 weight in kg / (height in meter)^2 both inclusive, who were judged as healthy on the basis of a pre-study physical examination and clinical laboratory tests.

Analytical methods

Analysis of darunavir was performed by HPLC/MS/MS.

This HPLC/MS/MS method involved the extraction of darunavir and the internal standard atazanavir from human plasma.

Storage period of study samples

After collection, the blood samples were placed in an ice bath until centrifugation and then placed in a refrigerated centrifuge within 30 minutes of blood sample collection, and then spun at 3000 rpm at 4°C for 15 minutes. The plasma was separated, transferred to labelled primary and secondary aliquots; primary aliquot was contained 1.5 ml of plasma and remaining amount was transferred in to secondary aliquot and stored in a freezer at – 70°C ±20°C at the clinical facility until shipment to analytical facility.

2112 samples were expected however 1863 blood samples were received (1776 samples to analyse for study and 87 samples of 7 drop outs for safety evaluation). The missing samples are accounted for in the dossier. 3 samples were re-assayed and the reason for their repeats was documented and presented.

Bioanalytical report

The bioanalytical report was submitted with 20% of the subject chromatograms presented as well as the method SOPs. Atazanavir was used as an internal standard (IS) and was sourced from Mylan Laboratories Limited India (99.9% purity). A certificate of analysis for the reference standards of Darunavir ethanolate (91.8% purity) and Atazanavir sulphate have been provided and are deemed acceptable. A certificate of analysis for ritonavir (99.2% purity) was also provided as this was used in the method considering the design on the study.

For the actual study the calibration curve range was Darunavir: 150.369ng/ml to 15036.840ng/ml.

Darunavir: Inter day batch accuracy: 95.11-103.70%, precision: 4.58-6.11%

Incurred Sample Reanalysis

144 samples were identified for incurred sample reanalysis. 99.31% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Validation of the test method

The method has been validated and partially revalidated twice.

Pharmacokinetic variables

Primary parameters: AUC_t and C_{max}

Secondary parameters: T_{max}, AUC_i, K_{el}, $t_{1/2}$ and $AUC_{\_\%Extrap\_obs}$

Bioequivalence criteria; The 90% confidence interval of the relative mean AUC_t and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

Descriptive statistics: Mean, Standard deviation, coefficient of variance, Median, Maximum and Minimum for all pharmacokinetic parameters were calculated.

Statistical analysis: Statistical analysis was performed on pharmacokinetic data of subjects using SASR statistical software (Version: 9.3 SAS Institute Inc, USA).

Analysis of Variance: Ln-transformed data of Cmax, AUCt & AUCi were evaluated statistically using the PROC GLM from SASR for difference due to treatment, period and sequence as a fixed effects and subject within sequence as a random effect.

The period and treatment effects were tested at 5% level of significance and the sequence effect was tested at 10% level of significance using the Mean Square Error as the error term.

Two One-Sided test for bioequivalence: Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for Ln-transformed data of Cmax, AUCt and AUCi.

Power: The power of the ANOVA test to detect a 20% mean difference between test and reference formulations was reported.

The 90% confidence interval of the relative mean Cmax and AUCt of the test to reference formulation for Ln-transformed data was to be within 80.00% to 125.00% for Darunavir.

Results

Table 1. Pharmacokinetic parameters for Darunavir 800mg n=37 (non-transformed values)

(Test Product: Darunavir Film Coated Tablets 800 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
Cmax (ng/ mL)	8730.763	1561.785	17.888
AUCt (ng.hr/ mL)	113232.373	34816.425	30.748
AUCi (ng.hr/ mL)	120611.105	36034.230	29.876

(Reference Product: PREZISTA® (*Darunavir) 800 mg Filmtabletten (Film coated tablets))

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
Cmax (ng/ mL)	8199.550	1655.820	20.194
AUCt (ng.hr/ mL)	101322.983	31519.683	31.108
AUCi (ng.hr/ mL)	107065.865	34564.925	32.284

Table 2. Statistical analysis for Darunavir 800mg n=37 (ln-transformed values)

Pharmacokinetic parameter	Geometric mean (Test)	Geometric mean (Reference)	Ratio (%)
Cmax (ng/ mL)	8608.930	8057.667	106.84
AUCt (ng.hr/ mL)	108222.331	97424.692	111.08
AUCi (ng.hr/ mL)	115655.051	102718.144	112.59
Pharmacokinetic parameter	**90% Confidence Intervals**	**Intra Subject CV (%)**	**Power**
Cmax (ng/ mL)	(102.44%;111.43%)	10.700	1.0000
AUCt (ng.hr/ mL)	(104.08%;118.56%)	16.632	0.9999
AUCi (ng.hr/ mL)	(105.33%;120.35%)	17.033	0.9998

Safety data

During the course of study safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (haematology, biochemistry, immunological tests, urine analysis), chest X-ray (within past six months) and ECG at baseline. Laboratory parameters (haematology and biochemistry) were reassessed at the end of last period of the study.

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations. There were no deaths or serious adverse events occurring during the course of the study. Ten adverse events were reported by ten subjects.

Subjects 04 and 32 were discontinued due to adverse event of abdominal pain. Subjects 23 and 31 were discontinued due to adverse event of Vomiting. Subject 24 was discontinued due to adverse event of Mouth Ulceration. Subjects 27 and 44 were discontinued due to adverse event of Diarrhoea. Subject 11 was dizzy however completed the study and subjects 14 and 20 encountered the adverse event after the study termination.

The subjects that encountered the adverse events completely recovered before the end of the study. No statistical significant differences between the test and reference treatments, for the incidence of subjects having experienced adverse events and for the incidence of adverse events were seen.

Conclusions

Based on the presented bioequivalence study, Darunavir 800mg film coated tablets of Mylan Laboratories Limited India is considered bioequivalent with Prezista (Darunavir) 800mg film coated tablets manufactured by Janssen-Cilag SpA Italy.

Study BA14101915-01 Study Title:

Single dose oral bioequivalence study of Darunavir film-coated Tablets 600 mg and 'PREZISTA' (Darunavir) Film tabletten (film-coated Tablets) 600 mg with co-administration of 'NORVIR' (Ritonavir) Film tabletten (film-coated Tablets) 100 mg in healthy adult human subjects under fed conditions.

Methods

This was a randomised, open-label, two-period, two-treatment, two-sequence, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Darunavir 600 mg film coated tablets (test manufactured by Mylan Laboratories Maharashtra India) and Prezista 600 mg film coated tablets (MAH: Janssen-Cilag International NV, Belgium and manufactured by Janssen-Cilag SpA, Italy) with co-administration of Norvir (ritonavir 100mg film coated tablets, MAH: AbbVie Ltd, UK and manufactured by Abbvie Deutschland GmbH) in 59 healthy, adult, male human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

Study design

Based on the randomised schedule and following an overnight fast of at least 8 hours in both periods each volunteer was served with a standardised breakfast on day 1, 2, 4 and 5 at about 30 minutes prior to dosing. A single oral dose of concomitant ritonavir (100mg) medication was administered to the subjects twice daily at an interval of 12 hours from Day 1 to Day 5 and a single 800mg oral dose of investigational product (test or reference) was administered to the subjects on day 3. Administration of the morning concomitant medication and investigational product was done simultaneously on day 3 of each period.

Subjects were dosed while in sitting posture with 240ml of ambient temperature water. During confinement (Day 1 to 5), a standard meal was served at least 04 hours after dosing of IP/dosing of morning concomitant medication. Drinking water was not permitted one hour before dosing on day 3 of each period (dosing of investigational product) and until one hour post dose. Further meals/snacks after 04 hours post dose of IP/dosing of morning concomitant medication were served at appropriate times. Meals/snacks/breakfasts of identical composition and similar quantities were provided at approximately same times in all the periods. The two periods were separated by a wash-out phase of at least 8 days.

Blood samples were taken at the following time points: pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 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, 48.00 and 72.00 hours after dosing. Blood sampling time adjustments are presented in the dossier.

Test and reference products

Darunavir Mylan film-coated Tablets 600 mg manufactured by Mylan Laboratories Ltd. (batch No. 2007189; Exp. Date: May 2016) has been compared to Prezista Film Coated Tablets 600 mg manufactured by Janssen-Cilag (Batch No: EGZ0D00, Exp. Date: May 2017

Population studied

60 healthy adult male human subjects were enrolled as per the protocol to ensure dosing of 52 subjects (power of the study). Only 59 subjects were dosed and 55 completed the study. The dropouts are discussed below however it is not clear if the samples from Subject No.: 17, 19, 32 & 35 were analyzed for Safety Evaluation.

Main inclusion criteria:

Healthy, non-smoking and non-tobacco using adult males and/or non-pregnant, non-lactating females of 18 to 45 years age both inclusive, a Body Mass Index (BMI) 18.5 to 30.0 weight in kg / (height in meter) ^{2} both inclusive, who were judged healthy on the basis of a pre-study physical examination and clinical laboratory tests.

Analytical methods

Analysis of darunavir was performed using HPLC/MS/MS method.

This HPLC/MS/MS method involved the extraction of darunavir and the internal standard Darunavir D9 from human plasma.

Storage period of study samples

After collection, the blood samples were placed in an ice bath until centrifugation and then placed in a refrigerated centrifuge within 30 minutes of blood sample collection, and then spun at 3000 rpm at 4°C for 15 minutes. The plasma was separated, transferred to labelled primary and secondary aliquots; primary aliquot was contained 1.5 ml of plasma and remaining amount was transferred in to secondary aliquot and stored in a freezer at – 70°C ±20°C at the clinical facility until shipment to analytical facility.

2880 samples were expected however 2736 blood samples were received. 2640 samples had valid results. The missing samples are accounted for in the dossier. 12 samples were re-assayed and the reason for their repeats was documented and presented.

Bioanalytical report

The bioanalytical report was submitted with 20% of the subject chromatograms presented as well as the method SOPs. Atazanavir was used as an internal standard (IS) initially and was later changed to darunavir D9 via partial revalidation. Darunavir D9 was sourced from Clearsynth Labs limited (98.65% purity). A certificate of analysis for the reference standards of Darunavir ethanolate (91.8% purity) and Darunavir D9 have been provided and are deemed acceptable. A certificate of analysis for ritonavir (99.2% purity) was also provided as this was used in the method considering the design on the study.

For the actual study the calibration curve range was Darunavir: 149.686ng/ml to 14968.553ng/ml.

Incurred Sample Reanalysis

192 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Validation of the test method

The method has been validated and partially revalidated five times. The following parameters were addressed;

Specificity and selectivity, Linearity including calibration curve, limit of quantification including accuracy and precision, ruggedness (different analyst, different column, accuracy and precision), precision (intra and inter day), accuracy (intra and inter day), recovering of the analyte and internal standard, matrix effect (specificity, selective and LOQ), anticoagulant effect, partial and whole batch re-injection reproducibility, dilution integrity including accuracy and precision, bench top stability coolant stability, refrigerator stability, dry extract stability in-injector stability, freeze thaw stability, short term and long term stock solution stability (of analyte and internal standard) at room temperature, at 2-8°C, as well as instrument ruggedness.

Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The lower limit of quantification (LLOQ) of this method for the estimation of Darunavir concentrations in plasma was 150.178ng/ml (Precision 1.56%, Accuracy 103.63%). The linearity range of Darunavir was from 150.178ng/ml to 15017.766ng/ml. (9 point curve)

Pharmacokinetic variables

Primary parameters: AUC_t and C_{max}

Secondary parameters: T_{max}, AUC_i, K_{el}, $t_{1/2,}$ and AUC_%Extrap_obs

Bioequivalence criteria; The 90% confidence interval of the relative mean AUCt and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

Descriptive statistics: Mean, Standard deviation, coefficient of variance, Median, Maximum and Minimum for all pharmacokinetic parameters were calculated.

Statistical analysis: Statistical analysis was performed on pharmacokinetic data of subjects using SASR statistical software (Version: 9.3 SAS Institute Inc, USA).

Analysis of Variance: Ln-transformed data of Cmax, AUCt & AUCi were evaluated statistically using the PROC GLM from SASR for difference due to treatment, period and sequence as a fixed effects and subject within sequence as a random effect.

The period and treatment effects were tested at 5% level of significance and the sequence effect was tested at 10% level of significance using the Mean Square Error as the error term.

Two One-Sided test for bioequivalence: Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for Ln-transformed data of Cmax, AUCt and AUCi.

Power: The power of the ANOVA test to detect a 20% mean difference between test and reference formulations was reported.

The 90% confidence interval of the relative mean Cmax and AUCt of the test to reference formulation for Ln-transformed data was to be within 80.00% to 125.00% for Darunavir.

Results

Table 3. Pharmacokinetic parameters for Darunavir 600mg; n=55 (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (± SD) N = 55	
	Reference product(R)	Test Product
*Tmax (h)	3.350 (1.330, 5.000)	3.330 (1.330, 5.030)
Cmax (ng/mL)	9394.126 (±2369.653)	9897.001 (±2813.589)
AUCt (ng.hr/mL)	115216.923 (±44071.519)	129990.274 (±55432.415)
AUCi (ng.hr/mL)	123703.787 (±45966.819)	138488.873 (±56621.192)
Kel (1/hr)	0.063 (± 0.026)	0.058 (± 0.021)
T½ (hr)	12.629 (± 4.417)	13.600 (± 4.923)
AUC_%Extrap_obs (%)	7.073 (± 4.208)	6.486 (± 4.985)
* For Tmax median (min – max)		

Table 4. Additional pharmacokinetic data for Darunavir

Record descriptor	Related information
$AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$	Subject#33,Period # 1, Test Subject#54,Period # 1, Test
Cmax is the first point	None
Pre-dose sample > 5% Cmax	None

Table 5. Statistical analysis for Darunavir 600mg n=55 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals		CV %
		Lower%	Upper%	
Cmax (ng/mL)	104.96 %	100.26 %	109.87 %	14.381 %
AUCt (ng.hr/mL)	112.29 %	105.55 %	119.46 %	19.532 %
AUCinf (ng.hr/mL)	111.56 %	104.89%	118.65%	19.456

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

Safety data

During the course of study the safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (haematology, biochemistry, immunological tests, urinalysis), chest X-ray (within past six months) and ECG at baseline. Laboratory parameters (haematology and biochemistry tests) were re-assessed at the end of last period of the study. In this study, all the out of range laboratory parameters were evaluated as clinically insignificant or clinically significant during post study assessment. The laboratory parameter which was labelled as clinically significant by the physician, was documented as an adverse event and repeated until it was reported clinically non significant or within the normal range in the follow up.

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations. A total of seven adverse events (AEs) were reported by seven subjects and all the adverse events were considered to be mild in nature.

There were two AEs (Dizziness and Headache) considered possibly related and one AE (Platelet count increased) considered remotely related to the oral administration of test product. There were three AEs (Headache, Eosinophil count increased and Blood triglycerides increased) considered possibly related and one AE (White blood cell count increased) considered remotely related to the oral administration of reference product.

The volunteers that encountered the adverse events completely recovered before the end of the study. No statistical significant differences between the TEST and REFERENCE treatments, for the incidence of subjects having experienced AEs and for the incidence of AEs were seen.

Conclusions

Based on the presented bioequivalence study Darunavir 600mg film coated tablets manufactured by Mylan Laboratories Limited India are considered bioequivalent with Prezista 600mg film coated tablets of Janssen-Cilag International NV, Belgium.

The results of study BA14101915-01 with the 600mg film coated tablet formulation can be extrapolated to Darunavir 75mg, 150mg, 300mg and 400mg.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The applicant has presented two bioequivalence studies using the 600mg and 800mg presentations. The results conclude that both test products are bioequivalent to the chosen reference product. The bio waiver criteria are fulfilled and some issues with respect to the chosen dissolution methods have been satisfactorily clarified.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study Darunavir 800mg film coated tablets of Mylan Laboratories Limited India is considered bioequivalent with Prezista (Darunavir) 800mg film coated tablets manufactured by Janssen-Cilag SpA Italy.

Based on the presented bioequivalence study Darunavir 600mg film coated tablets manufactured by Mylan Laboratories Limited India are considered bioequivalent with Prezista 600mg film coated tablets of Janssen-Cilag International NV, Belgium.

The results of study BA14101915-01 with the 600mg film coated tablet formulation can be extrapolated to Darunavir 75mg, 150mg, 300mg and 400mg (bio waiver criteria are fulfilled, whilst issues with respect to the chosen dissolution methods have been clarified).

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Severe Skin Reactions Hepatotoxicity Hyperglycaemia Lipid Abnormalities Pancreatitis

Summary of safety concerns	
	Fat redistribution Immune reconstitution inflammatory syndrome Development of drug resistance Overdose due to medication error Drug-drug interactions
Important potential risks	Coronary artery events Cardiac conduction abnormalities Convulsions Growth abnormalities in the paediatric population Off-label use of darunavir/cobicistat in the paediatric population and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL Renal toxicity of DRV/COBI Hyperbilirubinaemia
Missing information	Older people (65 years and above) Pregnant and breast-feeding women Subjects with severe hepatic impairment (Child-Pugh C) Subjects with renal impairment *Darunavir/Ritonavir* Long-term safety data in children from 3 to 17 years of age *Darunavir/Cobicistat* Use in children <18 years of age Long-term safety of darunavir/cobicistat in adults Subjects coinfected with HIV and HBV and/or HCV

Pharmacovigilance plan

No additional pharmacovigilance activities are required.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks: Severe Skin Reactions	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Section 2 and 4 of the PL contain adequate information on this safety concern.	None
Important identified risks: Hepatotoxicity	Section 4.2, 4.3, 4.4, 4.8 and 5.2 of the SPC contain adequate information on this safety concern. Section 2 and 4 of the PL contain adequate information on this safety concern.	None
Important identified risks: Hyperglycaemia	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Section 2 and 4 of the PL contain adequate information on this safety concern.	None
Important identified risks: Lipid Abnormalities	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Pancreatitis	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Important identified risks: Fat redistribution	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Section 2 and 4 of the PL contain adequate information on this safety concern.	None
Important identified risks: Immune reconstitution inflammatory syndrome	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Section 2 of the PL contains adequate information on this safety concern.	None
Important identified risks: Development of drug resistance	Section 4.1, 4.2, 4.3, 4.4 and 4.5 of the SPC contain adequate information on this safety concern.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Overdose due to medication error	Section 4.1 and 4.2 of the SPC contain adequate information on this safety concern. Section 2 of the PL contains adequate information on this safety concern.	None
Important identified risks: Drug-drug interactions	Section 4.3, 4.4 and 4.5 of the SPC contain adequate information on this safety concern. Section 2 of the PL contains adequate information on this safety concern.	None
Important potential risks: Coronary artery events	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Important potential risks: Cardiac conduction abnormalities	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Important potential risks: Convulsions	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Important potential risks: Growth abnormalities in the paediatric population	This safety concern is not listed as per the Mylan SmPC and PL for darunavir.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks: Unapproved use of darunavir/cobicistat in the children and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL (MedDRA PT term: Off label use)	Section 4.1, 4.2 and 4.4 of the SPC contain adequate information on this safety concern.	None
Important potential risks: Renal side effects of DRV/COBI	Sections 4.2, 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Important potential risks: Increased bilirubin in the blood	Section 4.8 of the SPC contains adequate information on this safety concern. Section 4 of the PL contains adequate information on this safety concern.	None
Missing information: Older people (65 years and above)	Section 4.2, 4.4 and 5.2 of the SPC contains information on limited experience in patients above the age of 65 year. Section 2 of PL addresses this limited experience in patients in this age group.	None
Missing information: Pregnant and breast-feeding women	Section 4.6 of the SPC contains information on the lack of experience in use in pregnancy and lactations. Section 2 of PL addresses this lack of information in use in pregnancy and lactations.	None
Missing information: Subjects with severe hepatic impairment	Section 4.2, 4.3 and 5.2 of the SPC contains information on the lack of darunavir use in subjects with severe hepatic impairment.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 2 of the PL contains adequate information on this safety concern.	
Missing information: Subjects with renal impairment	Section 4.2 and 4.4 of the SPC contains information on the lack of darunavir use in subjects with renal impairment.	None
Missing information: Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age	Section 4.8 and 5.1 of the SPC contains information on the lack of experience in this sub population.	None
Missing information: Darunavir/cobicistat: Use in children <18 years of age	Section 4.2 of the SPC contains information on the lack of experience in this sub population.	None
Missing information: Darunavir/cobicistat: Long-term safety in adults	Section 4.4 and 4.8 of the SPC contains information on the lack of long-term safety of darunavir use with cobicistat in adults.	None
Missing information: Darunavir/cobicistat: Subjects coinfected with HIV and HBV and/or HCV	Section 4.4 of the SPC contains information on the lack of darunavir use in subjects with severe hepatic impairment and also patienst with pre-eeixting liver dysfunction have an increased risk for liver function abnormalities. Section 4 of the PL contains adequate information on this safety concern.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable. However, an updated RMP shall be submitted within two months after Commission Decision to align with the ongoing RMP updates of the originator.

2.6. PSUR submission

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

2.7. Pharmacovigilance

Pharmacovigilance system

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

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to 'parent 'PIL A' Duloxetine Mylan hard gastro-resistant capsules and 'parent' PIL B Prezista 75mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of darunavir film-coated tablets formulation. The reference product Prezista, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Prezista, co-administered with cobicistat, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

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 studies conducted with 800 mg and 600 mg film-coated tablet formulations, form the pivotal basis, with an open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period crossover design. 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 Darunavir Mylan film-coated Tablet 600 mg met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The test formulation of Darunavir Mylan film-coated Tablet 800 mg met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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

4. Recommendation

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

75mg, 150mg, 300mg, 600mg tablets

Darunavir, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir Mylan tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with darunavir co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir.

400mg and 800mg tablets

Darunavir co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).

Darunavir Mylan tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).
- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir (see sections 4.2, 4.3, 4.4 and 5.1).

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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