



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prezista

International non-proprietary name: **darunavir**

Procedure No. **EMA/H/C/000707/X/46**

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



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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N V submitted on 22 February 2012 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Prezista 800 mg, film-coated tablets, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend c) of the Commission Regulation (EC) No 1234/2008.

Janssen-Cilag International NV. is already the Marketing Authorisation Holder for Prezista 75 mg, 150 mg, 300 mg, 400 mg, 600 mg, film-coated tablets and 100 mg/ml oral suspension (EU/H/C/1/06/380/001-006).

The applicant applied for the following indication: Treatment of human immunodeficiency virus (HIV-1) infection in adult patients as well as antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg body weight.

The application submitted is composed of administrative information, complete quality data, and a clinical bioequivalence study.

Information on Paediatric requirements

Not applicable

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

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.

Licensing status

Prezista has been given a Marketing Authorisation in European Union since 12 February 2007.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP: Barbara van Zwieten-Boot

- The application was received by the EMA on 30/01/2012.
- The procedure started on 22/02/2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 May 2012 (Annex 1).

- During the meeting on 18-21 June 2012, 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 21 June 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 September 2012.
- During the meeting on 15 – 18 October 2012, 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 Prezista 800 mg film coated tablets on 18 October 2012.

2. Scientific discussion

1.3. Introduction

PREZISTA (darunavir, DRV) is a protease inhibitor.

DRV is currently licensed for use in treatment-experienced patients at a dose of 600mg twice daily (b.i.d.), with ritonavir 100mg b.i.d., in combination with other antiretroviral medicinal products.

The once daily (q.d.) 800mg dosing regimen of DRV in combination with ritonavir 100 mg qd and other antiretroviral medicinal products is approved for the treatment of ARV-naïve adult patients as well as for ARV-experienced adults with no DRV resistance associated mutations and who have plasma HIV-1 RNA < 100.000 copies/ml and CD4+ cell count ≥ 100 cells $\times 10^6/l$.

Furthermore, DRV is licensed for use in ART-experienced paediatric patients from the age of 3 years and at least 15 kg body weight with a recommended dose of DRV based on body weight.

Janssen-Cilag International NV applied for a line extension of the original Prezista Marketing Authorisation concerning a new tablet strength (800 mg). This new strength has been developed to simplify the currently approved dosing regimen of darunavir 800 mg once daily (q.d.) in combination with low-dose ritonavir (rtv). Specifically, one 800-mg tablet can be administered instead of two 400-mg tablets.

The application is supported by the data from Phase I studies, in which the bioavailability and bioequivalence, respectively, of 2 tablets of the reference 400-mg tablet formulation and 1 tablet of the 800-mg tablet formulation was assessed. These studies serve to bridge the new tablet strength to the clinical safety and efficacy established in the original Prezista marketing authorisation.

The drug substances and excipients used in the manufacture of new strength are identical to those used in the manufacture of the currently approved product strengths, with the exception of hypromellose and purified water for the wet granulation and Opadry II Dark red for the new coating.

Concerning the chemical-pharmaceutical information reference is made, in several sections, to the information already provided for the already authorised strengths.

1.4. Quality aspects

1.4.1. Introduction

The product is presented as film coated tablets containing a new strength of 800 mg of darunavir (as ethanolate) as active substance.

The composition is described in section 6.1. of the SmPC.

The product is available in Opaque high density polyethylene (HDPE) plastic bottle fitted with polypropylene (PP) child resistant closure

1.4.2. Active Substance

The active substance used in the 800 mg film coated tablets , darunavir (as ethanolate), is the same active substance as that approved for the currently authorised film coated tablets strengths.

1.4.3. Finished Medicinal Product

Pharmaceutical Development

The 800 mg film coated tablet was developed to further address clinical needs. This additional strength allows a single film coated tablet taken once daily.

The 800 mg film coated tablets are manufactured with the currently approved active substance which is also used for the other already authorised strengths. Accordingly, the formulation development was undertaken to produce an 800mg film coated tablet of a suitable size for dosing. Because of the high drug load for this tablet and feasibility tests using a direct compression blend failed, fluid bed granulation was identified as the most suitable technology for manufacture. Formulation optimization studies were performed with granulation mixtures with different amount of hypromellose binder and the amount of filler silicified microcrystalline cellulose in the external phase. A design of experiment (DoE), in which the quantities of the functional excipients were varied at 80 to 120% of the preliminary selected target concentration levels, has been performed to assess the robustness of the formulation. The study confirmed the robustness of the selected formulation composition towards the quality attributes of the tablet.

The use of the new tablet strength is supported by the results of Phase I studies, in which the bioavailability and bioequivalence, respectively, of 2 tablets of the reference 400-mg tablet formulation and 1 tablet of the 800-mg tablet formulation was assessed.

The only new excipients, compared to the other film coated tablet strengths, are hypromellose and purified water for the wet granulation and Opadry II Dark red for the new coating. An in-house specification is applied for the commercially available film-coating. The other excipients, comply with the Ph Eur.

The container consists of a white, high-density polyethylene (HDPE), bottle with child-resistant polypropylene (PP) closure with induction seal liner. Drawings and specifications were provided. It was declared that the bottle/closure package can be designated as child-resistant and suitable for adults, certified according to ISO 8317. The proposed container is made of the same materials as used for the other authorised strengths.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of this new strength.

Manufacture of the product

Prezista 800mg tablets are prepared by a wet granulation process, followed by milling of the granulate, final blending, compression, film coating, and packaging.

A blend of the granulate and the external phase excipients is compressed using a conventional rotary press, and tablet cores are coated, which together with the tablet dimensions and debossing, help to distinguish the new strength from the currently authorised strengths.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in process controls are adequate for this film coated tablet preparation.

The batch analysis data shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications include appropriate tests for appearance, identification (HPLC, IR), assay (HPLC, 95.0-105.0%), chromatographic purity (HPLC), uniformity of dosage units (Ph. Eur.), dissolution, and microbiological purity (Ph. Eur.).

Batch analysis results in 3 full-scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of 3 batches stored under long term conditions for 12 months at 25°C/60%RH and 30°C/75%RH and for up to 6 months under accelerate conditions at 40°C/75%RH according to ICH guidelines were provided. An in-use stability study was performed in one batch, the bottles were stored at 25°C/60% RH and 30°C/75%RH opened every day (5 days per week) for a period of 2 months; after this period, the bottles were stored for an additional 1 month prior to the start of testing. Additionally photostability, temperature cycling, and 50°C studies (3 months) were performed.

The batches of Prezista 800 mg film coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay (HPLC), chromatographic purity (HPLC), assay of ethanol (GC), dissolution (HPLC), water Content (KF), stereo-isomeric purity (HPLC) and microbiological purity. The stability test methods are identical to the testing methodology applied for release testing. In addition, stereo-isomeric purity (in one batch), ethanol, and water content are also determined for information. The analytical procedures used were stability indicating.

Based on available stability data, the proposed shelf-life as stated in the SmPC are acceptable.

1.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of this new strength Prezista 800 mg film coated tablets 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 the clinic.

1.4.5. 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.

1.4.6. Recommendation(s) for future quality development

Not applicable

1.5. Non-clinical aspects

1.5.1. Introduction

The 800 mg Prezista film coated tablets is considered not to present any nonclinical safety concerns additional to those already encountered with administration of the approved Prezista film coated tablets in humans. Thus, no non-clinical studies have been performed to support this new application. This was acceptable to the CHMP.

1.5.2. Ecotoxicity/environmental risk assessment

The Applicant has submitted an ERA, updated to include the 800mg, but no new studies have been performed for this application. This is considered acceptable as this line-extension concerns additional tablet strength, so the patients will be dosed with one single tablet instead of two, a change which will not lead to an increase in use or environmental exposure.

1.6. Clinical aspects

1.6.1. Introduction

GCP

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

- Tabular overview of clinical studies

Study No. (Country)	Study Objective	Study Design	Type of Subjects Total No. (M/F) Entered/Completed
TMC114-C176 (Germany)	To establish the bioequivalence of a 800-mg tablet formulation of DRV to that of the commercial 400-mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions.	Open-label, randomized, 2-way crossover trial in 2 panels	Healthy volunteers 128 (82/46) 128/121
TMC114-C182 (Poland)	To compare the oral bioavailability of a 800-mg tablet formulation of	Open-label, randomized, crossover trial in	Healthy volunteers 32 (22/10)

Study No.	Study Objective	Study Design	Type of Subjects
	darunavir to that of the commercial 400-mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions.	2 panels	32/32

1.6.2. Pharmacokinetics

Formulation

The direct compression formulation powder blend used in the currently marketed 75-mg, 150-mg, 400-mg, and 600-mg tablets, if compressed to produce an 800-mg tablet, would result in a tablet that is too large to be swallowed comfortably by patients. Hence, formulation development was undertaken to produce an 800-mg tablet with a suitable size for dosing and after appropriate testing; a wet granulation formulation was selected.

Study TMC114-C182

Study TMC114-C182 was an open-label, randomized, crossover trial in 2 panels.

The objective was to compare the oral bioavailability of a 800-mg tablet formulation of darunavir to that of the commercial 400-mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions.

The following dose regimens were administered:

- Panel 1
 - Treatment A: darunavir 800 mg single dose (2 × 400 mg tablet formulation F030) under fed conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
 - Treatment B: darunavir 800 mg single dose (1 × 800 mg tablet formulation F002) under fed conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
- Panel 2
 - Treatment C: darunavir 800 mg single dose (2 × 400 mg tablet formulation F030) under fasting conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
 - Treatment D: darunavir 800 mg single dose (1 × 800 mg tablet formulation G002) under fasting conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;

Under fed conditions, the tablets were administered within 10 min after completion of a standardised breakfast. A washout period of 7 days was applied between the periods.

Blood samples are taken up to 72 hours after administration for darunavir and up to 24 h after administration for ritonavir. Plasma was analysed for darunavir and ritonavir using a validated LC-MS/MS method with a lower limit of quantification (LLOQ) of 5 ng/ml.

Thirty two healthy volunteers, 22 males and 8 females, aged 18 – 47 years, were included in this study and received treatment under fasting or under fed conditions, i.e. 16 subjects per panel. All subjects completed the study and were included in the pharmacokinetic and statistical analysis.

For the analysis of darunavir and ritonavir, a previous validated analytical method has been applied. Selectivity was proven using plasma of 6 independent sources. No matrix effect is observed. Intra-run accuracy and precision and inter-run accuracy and precision were within the normal standard criteria. During analysis of study samples, intra-run performance and overall performance were within standard criteria.

The pharmacokinetics results for darunavir are shown in table 1. All darunavir pre-dose concentrations were below the limit of quantification (BLQ). T_{max} was not observed in the first sampling point. The ratio AUC_t/AUC_{inf} was well above 80%.

Ritonavir pre-dose concentrations showed that steady state was reached.

Table 1. Pharmacokinetics results for darunavir in Study TMC114-C182

Type of Subjects Total No. (M/F) Entered/Completed Age (yrs), Median (Range)	Treatments (Dose, Dosage Form, Route)			Mean Pharmacokinetic Parameters (SD) of DRV				LSmean Ratio (90% CI)	
				C _{max} [ng/mL]	t _{max} [h]	AUC _{last} [ng.h/mL]	t _{1/2term} [h]	C _{max}	AUC _{last}
Healthy volunteers 32 (22/10) 32/32 Panel I 23.0 (18-47) Panel II 26.5 (20-47) (0 dropouts)	<u>Panel 1</u> Fed conditions	RTV 100 mg, q.d. on Days 1-5	Treatment A single dose DRV 2 x 400-mg oral tablet fed	7790 (2137)	3.00 (1.50 – 4.00)	145559 (59296)	14.2 (4.1)	Test versus Reference	
			Treatment B single dose DRV 800-mg oral tablet fed	6993 (2227)	3.50 (1.50 – 5.00)	136472 (67188)	14.0 (4.0)	89.13 (82.62- 96.15)	91.66 (84.24- 99.73)
	<u>Panel 2</u> Fasted conditions	RTV 100 mg, q.d. on Days 1-5	Treatment C single dose DRV 2 x 400-mg oral tablet fasted	4931 (988)	2.00 (1.00- 5.00)	86391 (26147)	13.7 (5.6)	Test versus Reference	
			Treatment D single dose DRV 800-mg Oral tablet fasted	5301 (1302)	2.00 (1.50- 4.02)	93293 (26850)	17.0 (6.3)	106.20 (95.20- 118.48)	108.14 (93.76- 124.72)

Study TMC114-C176

Pivotal study C176 was an open-label, randomized, 2-way crossover trial in 2 panels

The objective of the study was to establish the bioequivalence of a 800-mg tablet formulation of DRV to that of the commercial 400-mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions.

The following dose regimens were administered:

- Panel 1
 - Treatment A: darunavir 800 mg single dose (2 × 400 mg tablet formulation F030) under fasted conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
 - Treatment B: darunavir 800 mg single dose (1 × 800 mg tablet formulation F002) under fasted conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
- Panel 2
 - Treatment C: darunavir 800 mg single dose (2 × 400 mg tablet formulation F030) under fed conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;
 - Treatment D: darunavir 800 mg single dose (1 × 800 mg tablet formulation G002) under fed conditions on day 3, and ritonavir 100 mg twice daily (b.i.d.) on days 1 to 5;

Under fed conditions, the tablets were administered within 10 min after completion of a standardised breakfast. A washout period of 7 days was applied between the periods.

Blood samples are taken up to 72 hours after administration for darunavir and up to 24 h after administration for ritonavir. Plasma was analysed for darunavir and ritonavir using a validated LC-MS/MS method with a LLOQ of 5 ng/ml.

For the analysis of darunavir and ritonavir, a previous validated analytical method has been applied. During analysis of study samples, intra-run performance and overall performance were within standard criteria. Incurred sample reanalysis showed good reproducibility.

One hundred and twenty eight healthy volunteers, 82 males and 46 females, aged 19 – 56 years, were included in this study and received treatment under fasting (n=83) or under fed conditions (n=45). Seven subjects did not complete the study due to AEs (n=2), withdrawal of consent (n=4) and non-compliance (n=1).

The pharmacokinetics results for darunavir are shown in table 2. All darunavir pre-dose concentrations were BLQ. Tmax was not observed in the first sampling point. The ratio AUCt/AUCinf was well above 80%.

Ritonavir pre-dose concentrations showed that steady state was reached.

Table 2. Pharmacokinetics results for darunavir in Study TMC114-C176

Type of Subjects Total No. (M/F) Entered/Completed Age (yrs), Median (Range)	Treatments (Dose, Dosage Form, Route)			Mean Pharmacokinetic Parameters (SD) of DRV				LSmean Ratio (90% CI)	
				C _{max} [ng/mL]	t _{max} ¹ [h]	AUC _{last} [ng.h/mL]	t _{1/2term} [h]	C _{max}	AUC _{last}
Healthy volunteers 128 (82/46) 128/121 Panel I 41.0 (19-56) Panel II 41.0 (20-54)) Dropouts: 2 (AE) 4 (withdrew consent) 1 (non-compliance)	<u>Panel 1</u> Fasted conditions	RTV 100 mg, q.d. on Days 1-5	A single dose DRV 2 x 400-mg oral tablet fasted	4866 (1441)	2.02 (0.97- 23.93)	96120 (54820)	16.09 (8.377)	Test versus Reference	
			B single dose DRV 800-mg oral tablet fasted	4914 (1332)	2.00 (1.00- 4.98)	91140 (40250)	16.96 (17.19)	101.97 (98.03- 106.07)	99.18 (94.35- 104.27)
	<u>Panel 2</u> Fed conditions	RTV 100 mg, q.d. on Days 1-5	C single dose DRV 2 x 400-mg fed	7031 (1669)	2.98 (1.00- 5.97)	105900 (32530)	13.45 (4.771)	Test versus Reference	
			D single dose DRV 800-mg fed	6773 (1668)	2.98 (0.97- 5.00)	105100 (37880)	14.03 (4.622)	95.50 (92.15- 98.97)	97.59 (93.82- 101.51)

1.6.3. Discussion on pharmacokinetics

To support the pharmacokinetics/bioavailability of the 800 mg tablet, a relative bioavailability study TMC114-C182 in healthy subjects, comparing the 800 mg tablet vs. the 400 mg tablet and a pivotal bioequivalence study TMC114-C176 in healthy subjects, comparing the 800 mg tablet vs. the 400 mg tablet were conducted.

The pharmacokinetic results from study TMC114-C182 show that the rate and extent of absorption were similar between intakes of a single 800 mg dose of darunavir formulated as one 800-mg tablet (G002) or two 400-mg commercial tablets (F030). Under fed and fasted conditions the 90% CI for C_{max} and AUC_{last} were within the limits of bioequivalence. The 90% CI for AUC_{inf} was outside the limits of bioequivalence. The administration of darunavir/ritonavir with food resulted in higher exposures of darunavir relative to administration in the fasted state in both treatment groups consistent with historical data. The pharmacokinetic parameters for ritonavir were comparable across formulations, but food intake had a pronounced effect as both C_{max} and AUC_{24h} decreased under fed conditions. This is in line with historic data.

The pharmacokinetic results from study TMC114-C176 show that the rate and extent of absorption were similar between intake of a single 800 mg dose of darunavir formulated as one 800-mg tablet (G002) or two 400-mg commercial tablets (F030). Under fed and fasted conditions the 90% CI for C_{max}, AUC_{last} and AUC_{inf} were within the limits of bioequivalence. The administration of darunavir/ritonavir with food resulted in higher exposures of darunavir relative to administration in the fasted state in both treatment groups consistent with historical data. The pharmacokinetic parameters for ritonavir were comparable across formulations, but food intake decreased both C_{max} and AUC_{24h}. This is also in line with historic data.

1.6.4. Conclusions on clinical pharmacology

In the pivotal study C176, the bioequivalence of a 800 mg tablet formulation is evaluated versus the commercial 400 mg tablet formulation, under fasting and fed conditions. One hundred twenty eight healthy volunteers, 82 males and 46 females, aged 19 – 56 years, were included in this study and received treatment under fasting (n=83) or under fed conditions (n=45). Blood samples were taken up to 72 hours after administration for darunavir and up to 24 h after administration for ritonavir. Plasma was analysed for darunavir and ritonavir using a validated LC-MS/MS method with a LLOQ of 5 ng/ml. The pharmacokinetic results from this study show that the rate and extent of absorption were similar between intake of a single 800 mg dose of darunavir formulated as one 800-mg tablet or two 400-mg commercial tablets. Under fed and fasted conditions the 90% CI for C_{max}, AUC_{last} and AUC_{inf} were within the limits of bioequivalence.

The administration of darunavir/ritonavir with food resulted in higher exposures of darunavir relative to administration in the fasted state in both treatment groups consistent with historical data.

The pharmacokinetic parameters for ritonavir were comparable across formulations, but food intake decreased both C_{max} and AUC_{24h}. This is also in line with historic data.

In summary, bioequivalence was shown in study TMC114-C176 for a single dose of 800 mg DRV when given as either two 400-mg tablets (approved formulation) or as one 800-mg tablet, both under fed and fasted conditions and together with rtv 100 mg q.d.

1.7. Clinical efficacy

Not applicable in this application.

1.8. Clinical safety

Safety data were obtained from healthy subjects participating in the relative bioavailability study TMC114-C182 (n=32) and pivotal bioequivalence study TMC114-C176 (n=124), following a single dose of 800 mg DRV, formulated as 2 x 400-mg F030 tablets or 1 x 800-mg G002 tablet in the presence of low-dose rtv.

No deaths, other serious adverse events (SAEs), or AEs leading to treatment discontinuation were reported during the study occurred in study TMC114-C182. One subject experienced SAEs (humerus and radius fracture) and prematurely discontinued because of these SAEs within study TMC114-C176. Additionally, 1 subject prematurely discontinued because of non-serious AEs (abdominal pain and diarrhea) during the rtv phase of the first session. In addition, 1 subject reported a skin event of interest (grade 1 rash starting on Day 6 in the DRV + rtv phase of Session I). These SAEs, AEs leading to discontinuation, and skin event of interest all occurred in Panel 1 (fasted Darunavir conditions), and none of these events were considered related to DRV. The events of abdominal pain and diarrhea started prior to the first intake of DRV in Session I and were considered possibly related to rtv by the investigator.

In general, no consistent differences in the overall incidence of AEs were observed between the rtv phase and rtv + DRV phase for either panel or either treatment group. Most frequently observed AE in both studies was headache.

No relevant differences in incidence of headache were observed between the 2 DRV formulations in either panel. Within study TMC114-C176 including the larger population, AEs considered possibly related to DRV were reported in 17 subjects (20.5%) receiving DRV + rtv under fasted conditions and in 14 subjects (31.1%) receiving DRV + rtv under fed conditions, with no relevant differences between both formulations of DRV. This concerned mainly the events of headache and fatigue. Other AEs considered possibly related to DRV were reported in no more than 2 subjects per treatment phase. No AEs were considered probably or very likely related to DRV by the investigator.

Median changes in laboratory parameters, vital signs and electrocardiogram (ECG) parameters were generally small and not considered clinically relevant. No abnormalities were reported as AEs.

1.8.1. Discussion on clinical safety

The current safety data of the DRV 800-mg G002 tablet appear in line with the known safety profile of DRV and did not raise new safety signals. Although data are limited, there are no indications based on the formulation of the tablet or the phase I studies that warrant further consideration, or raise any concern on a potential worse safety profile of the current formulation compared to that of existing formulations.

A line extension usually may trigger the re start of the PSUR cycle. However, in the view of the safety profile of the 800mg tablet, the applicant has submitted a justification for not re starting the PSUR cycle which has been endorsed by the CHMP.

1.8.2. Conclusions on the clinical safety

The data generated from Phase I studies TMC114-C182 and TMC114-C176 demonstrated no relevant difference in safety between the DRV 800-mg tablet and the two 400-mg tablets (approved formulation).

1.9. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

RMP version 13.0 of 27 January 2012 was submitted with this procedure. However, since the start of the procedure, the MAH submitted version 15 of the RMP of 12 August 2012, including consideration of the new formulation proposed, with the Type II variation II-52, a variation to add the potential drug interaction with raltegravir to the currently approved Prezista label. The RMP is currently assessed with the Type II variation and will be finalised and approved with the named variation.

1.10. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- Full user testing in compliance with the above mentioned legislative requirements was performed (n=37 participants) on the initial patient leaflet for Prezista 300 mg filmcoated tablets, that was approved on 12 February 2007;
- With the additional strength of 800 mg, no new route of administration is proposed;
- No other changes than those related to this strength are introduced.

3. Benefit-Risk Balance

Benefits

DRV 800-mg tablet strength would simplify the approved dosing regimen of DRV 800 mg once daily (q.d.) in combination with low-dose ritonavir (rtv) 100 mg q.d., and other antiretroviral (ARV) products as it would reduce the number of DRV-containing pills from 2 (2 x 400-mg) to 1 (1 x 800-mg) per intake.

In study TMC114-C176, bioequivalence was shown for a single dose of 800 mg DRV when given as either two 400-mg tablets (approved formulation) or as one 800-mg tablet, both under fed and fasted conditions and together with rtv 100 mg q.d.

Risks

The data generated from Phase I studies TMC114-C182 and TMC114-C176 demonstrated no relevant difference in safety between the DRV 800-mg tablet and the two 400-mg tablets (approved formulation).

Benefit-risk balance

The overall B/R of Prezista 800 mg tablets (darunavir) is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Prezista in the treatment of human immunodeficiency virus (HIV-1) infection in adult patients as well as antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg body weight when co-administered with low dose and other antiretroviral medicinal products is favourable and 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).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the European Medicines Agency.

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

Not applicable