European Medicines Agency

London, 20 November 2008
EMEA/CHMP/637631/2008

ASSESSMENT REPORT FOR PREZISTA

International Nonproprietary Name:
darunavir

Procedure No. EMEA/H/C/707/X/16

Marketing Authorisation Holder (MAH): Janssen-Cilag International NV

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. Introduction

As of the end of 2007, an estimated 33.2 million people worldwide – 30.8 million adults and 2.5 children younger than 15 years – were living with HIV/AIDS. Approximately 50% of adults living with HIV/AIDS are women. An estimated 2.5 million new HIV infections and 2.1 million AIDS deaths occurred worldwide during 2007 (Source: UNAIDS).

Current options for the treatment of HIV-1 infected patients are:

- Nucleoside/tide analogue reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Fusion or entry inhibitor
- Integrase inhibitor
- CCR5 receptor antagonist

For treatment-naïve patients, a triple regimen is considered standard of care. The goal is to achieve effective suppression of viral replication below the detection limits of the available tests, thereby strongly reducing the emergence of resistance.

The use of PIs has been a major breakthrough in the therapy for HIV-1 infection, substantially reducing morbidity and mortality in infected individuals. However, the long-term use of the currently licensed PIs is often hampered by different factors such as poor compliance due to a high pill burden and food restrictions, side effects with impact on the quality of life and the emergence of resistant virus that is no longer inhibited by the medicinal product used.

As a consequence of side effects and resistance emergence, patients often switch between various HIV medications. Whilst new therapies have significantly simplified and enhanced the efficacy of antiretroviral (ARV) regimens in treatment-naïve patients, resistance and the resulting inability to achieve suppression of viral replication remain a significant problem affecting large numbers of patients. Resistance can be addressed by development of medicinal products with a different mechanism of action or by development of potent medicines with substantial barriers to cross-class resistance.

Darunavir is an inhibitor of wild type and mutant HIV-1 protease without inhibiting human cellular proteases. The activity has been demonstrated on laboratory strains and clinical isolates of HIV-1 and HIV-2, and it has been found to be efficacious and safe in treating HIV-1 infection in treatment experienced adult patients, including those that have been highly pre treated. The CHMP issued a positive opinion on the latter indication. The present submission for the 400 mg tablets evaluates the efficacy, safety and tolerability of darunavir in patients who are treatment naïve.

The PI darunavir (TMC114) is a close analogue of amprenavir (APV). The binding of darunavir to the wild-type protease was 87-fold greater than that of APV versus 33- fold more tightly than APV in the case of multi-drug resistant protease. Darunavir binds also more tightly to HIV-1 proteases than the protease inhibitors indinavir, ritonavir, nelfinavir, saquinavir, amprenavir, lopinavir, and atazanavir.

Darunavir 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 current submission addresses Follow-Up Measure (FUM) 24: “Week 48 study report from TMC114-C211, a randomised, controlled open-label trial to compare the efficacy, safety and tolerability of TMC114/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects” resulting in a new proposed indication for which the dose regimen requires a 400 mg tablet.

The MAH proposed the following therapeutic indication for the 400 mg film-coated tablet:

> *PREZISTA, co-administered with 100 mg ritonavir in combination with other antiretroviral medicinal products is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.*

This covers a broader population than the target population of the clinical trial submitted within this submission, namely ARV-naïve patients. It also includes the population of treatment experienced adults, which, however, are subject to a different posology and not covered by any clinical data submitted in this extension application.

Proposed posology:

> *In protease inhibitor naïve adults: The recommended dosage of PREZISTA is 800 mg once daily (q.d.) taken with ritonavir 100 mg q.d. and with food.*
>
> *Therapy should be initiated by a physician experienced in the management of HIV infection.*
> *PREZISTA must always be given orally with 100 mg ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products.*
> *The type of food does not affect the exposure to darunavir.*

The new indication is based on Week -48 analyses of plasma HIV RNA levels and CD4+ cell count from one open-label controlled trial comparing darunavir/ritonavir, with lopinavir/ritonavir given in combination with an optimised antiretroviral background treatment.

The following guidelines are applicable for the current application:

- Guideline on the clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02, Rev. 1)
- Choice of a Non-Inferiority Margin (CPMP/EWP/2158/99)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Points to Consider on Adjustment for Baseline Covariates (CPMP/EWP/2863/99)
- Points to Consider on Missing Data (CPMP/EWP/1776/99)

A Paediatric Investigation Plan was submitted September 2007 and has received a positive opinion in June 2008.

No Scientific Advice from any European regulatory authority including the EMEA was requested by the Company within the framework of the current submission.

- User consultation

The MAH considered it justified that no new user testing was performed for this application based on the following elements:

- 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 film-coated tablets that was approved on 12 February 2007;
- with the proposed indication extension to include antiretroviral naïve patients no new route of administration is proposed;
- with the proposed indication extension the target group of users (i.e. HIV-1 infected patients) will not fundamentally change.

The CHMP considered the MAH's argumentation to be acceptable and agreed that no new user consultation had to be provided.

2. Quality aspects

Introduction

The medicinal product Prezista 400 mg is presented as light orange film-coated tablets containing darunavir as darunavir ethanolate in a dosage of 433.64 mg, corresponding to 400 mg darunavir.

The other ingredients include microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, poly(vinyl alcohol) – partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc and sunset yellow FCF (E110).

The tablets are packed in high-density polyethylene (HDPE) bottles closed with polypropylene (PP) child resistant closures.

Active Substance

The active substance is darunavir. It is manufactured in solvated form as darunavir ethanolate, an established substance not described in any pharmacopoeia. Darunavir ethanolate is a hygroscopic substance, which is very slightly soluble in aqueous solutions. The active substance possesses 5 chiral centres [1S,2R,3aS,4S,6aR] and stereochemical purity is controlled by adequate specifications on stereochemical purity of the starting materials.

Full documentation on the active substance has already been assessed within the original Marketing Authorisation Application (MAA) for Prezista 300 mg. For this line extension to add the 400 mg strength, the MAH has only submitted new data on the active substance manufacturers and manufacturing process, the active substance specifications and justifications for the amended specifications and the active substance stability.

- Manufacture

The purified active substance is produced by a 4 step process, out of two starting materials. For the manufacturing process reference is made to the already marketed 300 mg Prezista. For the manufacturing of the 400 mg strength, an additional active substance manufacturer has been introduced. This manufacturer applies a different method of drying, resulting in a different particle size distribution of the active substance. Due to this change, the formulation of the finished product needed to be modified in order to keep flow characteristics of the blend at an acceptable level. Bioequivalence / Bioavailability studies have been performed with modified formulations.

- Specification

The active substance specification has been established in-house by the MAH. The MAH has justified the acceptance criteria for the particle size of the active substance by submission of laser diffraction patterns of the active substance batches used in clinical studies.

For both the approved and the proposed additional manufacturing site, batch analytical data demonstrating compliance with the active substance specification have been provided for at least 3 full scaled batches. The data demonstrate consistency in the manufacturing process and compliance with the proposed active substance specifications.

- Stability

Active substance stability data from one active substance manufacturer has already been assessed in the original MAA for the 300 mg strength. For this line extension application, the MAH submitted

long term stability data from 3 full scale batches manufactured at the additional production site. The results cover 3 months at 30°C/65%RH and 40°C/75%RH.

The manufacturing of the active substance at the new manufacturing sites does not lead to changes in the impurity profile of the substance. Also, the container closure system remains the same. It is thus not expected to affect the stability of the substance. The particle size distribution is not expected to affect the stability of the active substance either. The currently approved active substance retest period for the 300 mg is therefore approvable for both manufacturing sites. No special storage conditions are necessary.

Medicinal Product

The currently approved commercial dosage form for darunavir is a 300 mg orange film-coated tablet. To address unmet clinical needs, the additional 400 mg (light orange) strength has been developed.

The 400 mg tablets are prepared from a formulation that is qualitatively the same as that used for the approved commercial 300 mg tablet, incorporating all the same ingredients, with a minor decrease in the percentage of microcrystalline cellulose, and a corresponding minor increase in the percentages of colloidal anhydrous silica and magnesium stearate, to provide better powder flow properties for compression of the tablets (i.e. modified formulation). Multiple strengths of the modified formulation can be compressed from a common powder blend.

- Pharmaceutical Development

The development of the 400 mg tablets was based on the 300 mg tablets. However, the MAH has introduced an adapted formulation for the 400 mg strength. The provided justification for adapting the formulation in view of manufacturability issues, due to a change in particle size of the drug substance is considered adequate.

In total, 14 different formulations were evaluated. The test formulations varied slightly from the current 300 mg tablet formulation and were manufactured with mechanically dried active substance lots having a small particle size and reduced flow properties. For each formulation, the physical properties of the final blend (particle size, flowability, volume) and the tablet cores (appearance, weight, hardness, disintegration time, friability) were measured. Results from the current formulation manufactured with a statically dried (i.e., good flowing) active substance lot were used as the baseline. The currently proposed formulation was identified as having improved manufacturability: improved flow properties and/or a reduced tendency for sticking without risk of blend flow obstruction or tablet sticking on scale-up.

The qualitative composition of the 400 mg strength is identical to the already approved 300 mg tablets. Only a minor change in quantitative composition has taken place. The pharmaceutical development of the product has been adequately performed.

- Adventitious Agents

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

- Manufacture of the Product

The manufacturing process consists of blending the tablet core components, direct compression of the tablets and coating of the tablet cores. The manufacturing process can be considered as standard. Adequate in-process controls are proposed and the critical aspects of the manufacturing process (e.g. particle size, manufacturability, drug substance content of 52%) are adequately dealt with.

Batch analysis results support the view that active substance dosage, uniformity of content, degradation products and chromatographic purity, dissolution, and microbiological purity are adequately controlled. The Process Validation Scheme proposed by the MAH is appropriate.

- Product Specification

Appropriate medicinal product specifications have been set. The specifications for the finished product at release and shelf life are classical for this pharmaceutical form and include tests for appearance, identity, assay, degradation, dissolution, microbiological purity and uniformity of dosage units. The excipients used in the medicinal product comply with pharmacopoeial requirements or national standards where applicable. The proposed test parameters and acceptance criteria are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed site for commercial production have been provided on 2 pilot scaled development batches and 2 production scaled batches, demonstrating compliance with the release specification.

- Stability of the Product

The stability studies include long term and accelerated studies, bulk tablet studies, in-use studies, photostability studies and some auxiliary studies.

The performed stability studies follow a bracketing design that incorporates the not yet marketed high (600-mg) and the low (75-mg) strengths of the modified formulation tablets, the various package sizes and counts, and the tablet colours under development. The bracketing approach has been adequately justified.

Stability data have been provided for 3 pilot scaled batches of 75 mg tablets and 6 pilot scaled batches of 600 mg tablets filled in two sizes of containers. The batches have been stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) in the proposed container. The conditions used in the stability studies are according to the ICH stability guideline; several additional conditions have also been tested.

Several supportive studies have been performed. Data covering 24 months have been provided for 2 batches of modified 300 mg tablets and 9 month data of modified 400 mg tablets stored at ICH long term and accelerated conditions.

During all of the above studies, the test parameters were shown to be stable at all test conditions. In view of the stability results, the proposed shelf-life, with no special storage condition, can be approved. The MAH has committed to submit additional stability data, covering the complete shelf-life.

Furthermore, in-use stability data has been provided demonstrating that the modified formulation is stable after opening the container (75 mg, 3 months and 600 mg, 1 month). Photostability studies show that the product is not sensitive to light. In view of the observed stability during the in-use trials with the modified formulation, no additional in-use storage conditions nor a separate in-use shelf-life are considered necessary for the 400 mg tablets.

The stability data are considered adequate and support the proposed shelf of life 24 months for the 400 mg strength.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the active substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

3. Non-clinical aspects – Environmental Risk Assessment

There were no new non-clinical data submitted within this extension application. However, with reference to already submitted data, an environmental risk assessment was provided.

The recommended dosage for the newly proposed patient group is darunavir 800 mg q.d. taken with ritonavir 100 mg and together with food. The currently approved dosage for ARV therapy experienced patients is 600 mg b.i.d. taken with ritonavir, also together with food. Therefore the total daily dose is lower in the new patient group (800 mg/day) than that currently authorised (1200 mg/day).

In the original dossier, the exposures to darunavir in animal species in the repeated dose studies was similar to, or lower, than that in man at the clinical dose and therefore safety margins were absent. This was so, despite the co-administration of ritonavir, which increased exposure to darunavir in rats and mice. The exposure margins were calculated using an AUC value of 121µg•h/ml in man after a dose of darunavir/ritonavir of 600/100 mg b.i.d.

In a sub study of study TMC114-C211 (the main clinical study submitted in support of the new strength and indication), the mean C_{max} values for darunavir at a dose of 800/100 mg q.d. for 4, 24 and 48 weeks with a fixed background regimen in treatment-naïve HIV-1 infected subjects were 5.5, 5.8 and 6.8 µg/ml, respectively, with AUC_{24h} values being 64.2, 66.9 and 75.6 µg•h/ml at these same time points.

The C_{max} and AUC values were lower in this group of patients than the values of 10µg/ml and 121µg•h/ml for C_{max} and AUC that were previously reported at the recommended clinical dose of 600/100 mg b.i.d.

Therefore the pharmacokinetics of the new dosage regimen in the new patient population were within the values previously obtained and although safety margins are lacking, they are not further eroded in this group of patients.

The environmental risk assessment dated February 2008 comprised Phase II Tier A environmental fate and effects analysis. The values given in the summary for $PEC_{surface\ water}$ and the PEC:PNEC ratios were different from those calculated in the body of the report. For example, the $PEC_{surface\ water}$ was stated to be 0.044µg/l in the summary, but in the rest of the report 6µg/l or 0.057µg/l, depending upon whether the default F_{pen} of 1% or a refined F_{pen} was used.

Therefore, the MAH was asked to comment on these differences. The different predicted environmental concentration (PEC) values in the summary and the body of the report (sediment toxicity study with Hyalella sp, Lumbriculus sp or Chironomus sp) was due to the fact that the summary was not updated with the newly calculated values in the body of the report (based on the new market penetration data forecast). A revised environmental risk assessment was submitted in June 2008 in the Extension Application for the 75 and 150 mg tablets (pending) and the values between the report and the summary were aligned. The overall conclusion on the environmental risk remained the same.

The guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) states that 'If a substance is not readily biodegradable and if the results from the water sediment study (OECD 308) demonstrate significant shifting of the active substance to the sediment, effects on sediment organisms should be investigated in Tier B. The criterion for sediment studies is met if more that 10% of the substance at any time point after or at 14 days is present in sediment.

In the biodegradation test (OECD 301B), the low rate of CO2 evolution suggested that darunavir is not readily biodegradable. The aquatic sediment studies conducted according to OECD 308 and submitted in fulfilment of FUM 13 showed a significant amount of the radioactivity accumulating as non-extractable bound residues in the sediments in both the aerobic and anaerobic studies. In both systems there was >40% of the applied dose as bound residues. Therefore an additional FUM was raised at

renewal of the conditional MA in November 2007, that a sediment toxicity study with Hyalella sp, Lumbriculus sp. or Chironomus sp. was required (FU2 013.1). In the meanwhile, these data were provided and the additional FUM was considered solved (conclusions adopted at the May 2008 CHMP).

4. Clinical aspects

GCP

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

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

Pharmacokinetics

Two bioequivalence studies were submitted. Study C167 showed that particle size of the active substance may be critical with regard to bioequivalence with the marketed tablet. However, it should be taken into consideration that this study was carried out under fasting conditions. Although in study C162 fed and fasting conditions were studied, the Test tablet used in this study also had a different particle size of the API.

Study C162 showed that Test tablet F032 with a certain particle size was bioequivalent with the marketed tablet F016, under fed and fasting conditions. The proposed 400 mg tablet was dose proportional with the 600 mg F032 tablet used in study C162 for which bioequivalence was proven.

As the pharmacokinetics of darunavir under boosted conditions was considered linear over at least the 400 – 1200 mg dose range, this requirement is fulfilled. The 600 mg tablet was manufactured at the same site as the 400 mg tablet. The 400 tablet has the same particle size of the API as the one in the 600 mg tablet. Furthermore, the extrapolation was supported by dissolution tests over the pH range of 1 – 6.8 (see also Quality part).

Clinical efficacy

- Dose response studies

The recommended dose was based on findings of the studies TMC114-C202 and TMC114-C213. These two studies were assessed in the context of the original MAA for highly ARV therapy experienced patients. The proposed dosage of 800 mg darunavir (DRV) with 100 mg ritonavir (rtv) q.d. was considered appropriate, since superior efficacy of DRV/rtv 800/100 q.d. in combination with an optimised background regimen (OBR) to other available PIs was found and also pharmacokinetic results of the present trial and above mentioned trials indicated that adequate exposures were obtained with the once-daily DRV/rtv dose regimen. Based upon the effect on the plasma viral load of the 800/100 mg q.d. dose, and the above mentioned exposure data, it was hypothesised to be sufficient for efficacy testing in the ART-naïve patient population. This rationale for the choice of a DRV/rtv dose regimen in treatment naïve patients is considered to be relatively weak; however, results of study C211 overcome these concerns.

In addition, the MAH has evaluated whether this regimen could be useful (and so more convenient) for the ART-experienced. As a consequence, the MAH has started a randomised, open label, phase III study to evaluate the efficacy and safety of the 800/100 mg q.d. compared to the 600/100 mg b.i.d. in treatment experienced patients.

- Main clinical study

The 48 week results from one efficacy study, TMC114-211, have been submitted in support of the proposed indication for the new 400mg strength tablet. For bioequivalence issues see above.

METHODS

Study TMC114-C211 (ARTEMIS) was an open label, multi-centre, randomised controlled phase III trial.

The primary objective of this study was to establish non-inferiority in virologic response of DRV/rtv to lopinavir (LPV)/rtv. Non-inferiority would be established if the lower bound of the 95% confidence interval (CI) for the difference between % response in the DRV/rtv group and the LPV/rtv group was no larger than -12%.

Secondary objectives were, amongst others, to evaluate safety and tolerability over 192 weeks, to evaluate the durability of virologic response over 192 weeks, to compare the immunologic response, to evaluate the PK/PD relationships, to evaluate the superiority for virologic response in case DRV was non-inferior, to evaluate the resistance characteristics, and to assess the population pharmacokinetics of DRV in this treatment-naïve population.

Subjects were randomised at baseline in a 1:1 ratio to DRV/rtv or LPV/rtv according to two stratification factors: screening plasma viral load (< 100000, ≥ 100000 copies/ml) and screening CD4+ cell count (< 200, ≥ 200 cells/µl). The trial was open label; the treatment given to the patient was known to investigator and patients due to operational and logistic reasons.

Many of the secondary objectives were difficult to measure in this trial set up due to the lack of blinding and the small effect of treatment expected on several endpoints, making the study population too small to measure these effects. Especially the results of the "patient reported outcomes", i.e. results from the quality of life questionnaires were considered to be of little value by the CHMP. Also, not blinding investigator or patient could still have introduced some bias in the primary endpoints; however, the MAH adequately demonstrated that the open label did not affect any of the major outcomes of the trial, including conclusions on efficacy and safety.

The study population consisted of HIV-1 infected, antiretroviral treatment naïve, male and female adults with a baseline viral load ≥ 5000 HIV-1 RNA copies/ml. The cut-off date for the primary efficacy analysis was set on 13 June 2007, at which patients in the trial had reached 48 weeks of treatment.

In total, 691 subjects were randomised to receive either 800 mg DRV q.d. with 100 mg rtv (345 subjects) or 800 mg LPV with 200 mg rtv (346 subjects) in combination with a fixed background treatment of 300 mg tenofovir disoproxil fumarate (TDF) q.d. and 200 mg emtricitabine (FTC) q.d.

Of note, approximately 25% of the subjects in the control group used a non-validated LPV/rtv 800/200mg q.d. dose regimen whereas the majority used the approved LPV/rtv 400/100mg b.i.d. dose regimen in Europe. This should be taken into account in the critical assessment of the results.

For the present application, the 48 week results of this trial have been assessed. The analyses of subjects and treatment information were conducted on the ITT population, unless otherwise specified. The OP (on-protocol) population, defined as the set of all randomised subjects who took trial medication and did not take any disallowed ARV medication for more than one week, was similar to the ITT (intent-to-treat) population; there were only 3 subjects less in the DRV/rtv arm in the OP population. Therefore, results from both the ITT and OP populations are very similar.

RESULTS

Baseline data

The two treatment groups were comparable concerning demographic and baseline disease characteristics, and genotyping. Some differences were observed in the presence of concomitant disease; these were not considered to have a relevant effect on the trial outcomes.

Outcomes and estimation

Primary efficacy endpoint results: Virologic response defined as a confirmed plasma viral load of < 50 copies/ml was similar up to Week 12 in the DRV/rtv and LPV/rtv treatment groups. Thereafter a greater percentage of subjects in the DRV/rtv exhibited viral suppression, with the difference seemingly increasing over time.

At Week 48, virologic response in the ITT population was 83.7% for the DRV/rtv group and 78.3% for the LPV/rtv group. The difference in virologic response between the treatment groups was 5.3% (95% CI: -0.5% - 11.2%):

	DRV/rtv			LPV/rtv			DRV/rtv - LPV/rtv		
	N1	N2	%	N1	N2	%	%	lower CI	upper CI
Primary Outcome: Confirmed response (<50)	**287**	**343**	**83.7**	**271**	**346**	**78.3**	**5.3**	**-0.5**	**11.2**
Secondary outcomes:									
Confirmed response (2LOG)	294	343	85.7	293	346	84.7	1.0	-4.3	6.3
Confirmed response (<400)	301	343	87.8	295	346	85.3	2.5	-2.6	7.6

N1 = number of responders N2 = number of subjects with data

Similar results were obtained for the OP population: the Week 48 virologic response was 83.8% for the DRV/rtv group and 78.3% for the LPV/rtv group; the difference between the treatment groups was 5.5% (95% CI: -0.4 - 11.4).

Since the lower bound of the 95% CI for the difference in % response between the DRV/rtv and the LPV/rtv group at week 48 was well above the determined Δ of -12%, non-inferiority of the virologic response to DRV/rtv compared with the virologic response of LPV/rtv 48 weeks after initiating treatment in HIV-1 infected treatment naïve patients was established.

Sensitivity analyses demonstrated that the findings were robust and consistent across different populations and imputation methods. Study TMC114-C211 provides sufficient evidence to support the proposed indication by demonstrating similar efficacy of DRV/rtv to LPV/rtv in the target population of treatment naïve HIV infected patients.

Superiority of DRV/rtv versus LPV/rtv in virologic response at 48 weeks was not found.

Secondary efficacy endpoint results (ITT): Virologic response expressed as the percentage subjects with confirmed plasma viral load < 400 copies/ml was similar in the two treatment groups at all time points. At week 48 non-inferiority of DRV/rtv (87.8%) to LPV/rtv (85.3%) was demonstrated, with the difference between the two groups being 2.5% (95% CI: -2.6% - 7.6%).

Similar results were obtained for virologic response expressed as the percentage subjects with confirmed decrease in plasma viral load ≥2 log10 copies/ml. The difference in virologic response between the DRV/rtv (85.7%) and LPV/rtv group (84.7%) at week 48 was 1.0 % (95% CI: -4.3% - 6.3%), demonstrating non-inferiority of DRV/rtv to LPV/rtv.

At 48 weeks the mean change in log10 viral load from baseline was -2.77 and -2.65 log_{10} copies/ml for the DRV/rtv and LPV/rtv treatment groups respectively. The estimated difference (ANCOVA) between the groups at week 48 was -0.09 log10 copies/ml (95% CI: -0.26 - 0.07). Similar results were found in the OP population.

The "time to virologic response", with response expressed as the percentage of subjects with confirmed plasma viral load <50 copies/ml, is similar between the two groups up to week 36 after which a higher virologic response rate was seen in the DRV/rtv group than in the LPV/rtv group. The proportion of subjects not achieving a plasma viral load < 50 copies/ml was lower in the DRV/rtv group than in the LPV/rtv group, and loss of virologic response over time occurred slightly less frequently in the DRV/rtv group than in the LPV/rtv group. At week 48 DAVG (time averaged difference) of log plasma viral load was similar for the DRV/rtv and LPV/rtv treatment groups, being -2.65 and -2.56 log_{10} copies/ml, respectively.

The mean change relative to baseline in CD4+ cell count at Week 48 was 154 x 10^6/L and 161 x 10^6/L for the DRV/rtv and the LPV/rtv group respectively. There was no evidence that the mean change for both groups was different (difference in means at week 48 = -7, 95% CI: -27 - 13). The level of CD8 cells decreased similarly to the increase in CD4+ and consequently the CD4+/CD8 ratio increased.

One subject in the DRV/rtv group with 2 DRV resistance associated mutations (RAMs) and one subject in the LPV/rtv groups with 3 LPV RAMs at baseline both demonstrated a virologic response at week 48. No outcomes were reported for the individuals with either 1 DRV RAM or 1 or 2 LPV RAMs at baseline. The percentage of virologic failures was lower in the DRV/rtv group compared to the LPV/rtv group. The development of mutations was studied in these virologic failures. In the DRV/rtv group 10 subjects who demonstrated virologic failure had matching baseline/endpoint genotypes, 18 in the LPV/rtv group did so. In none of the virologic failures in the DRV/rtv group developing PI-RAMS were identified. In the LPV/rtv group one subject had two additional PI RAMS at endpoint, which were not associated with loss in susceptibility to LPV. In the virologic failures of the DRV/rtv group one developing NRTI RAM was identified, associated with a decreased susceptibility to FTC. In the LPV/rtv group, two virologic failures with developing NRTI RAMs, and one subject with 2 additional developing PI RAMs at endpoint were identified. No other clear causes for virologic failure were identified; however, long term data are required to evaluate the further evolution of development of resistance in the ART naïve patient population.

Treatment compliance was similar in both groups as based on pharmacokinetic sampling. The proportion of subjects with DRV plasma concentrations below the detection limit was ≤ 3% at all time points, and the proportion of subjects with LPV plasma concentrations below the detection limit was ≤ 6% at all time points. When considering the Medication Adherence Self-Report Survey (MASRI) questionnaire outcome, adherence was slightly higher in the DRV/rtv group (84%) than in the LPV/rtv group (79%) at week 48.

Ancillary analyses: There was some variation in response to DRV/rtv and LPV/rtv according to region. In Europe there was less response in the DRV/rtv group compared with the LPV/rtv group (diff = -4.3; 95% CI: -15.5 - 6.9), whilst in other regions the response in the DRV/rtv group appears to be somewhat improved compared with the LPV/rtv group. A likely explanation for this difference is that in Europe the discontinuation rate for DRV/rtv (13.0%) is higher than for LPV/rtv (10.0%) whereas for the other regions the discontinuation rate for DRV/rtv is lower than for LPV/rtv. It should be noted that the numbers in these groups were small and the differences between treatment arms not significant. Finally, for a part the regional differences can be explained by the use of non-validated once daily dosing of the comparator (Kaletra), see below.

Both baseline plasma viral load (VL) and baseline CD4+ cell count were considered as covariates; the randomisation was done accordingly as was the analysis. Patients with a higher baseline viral load (≥ 100000 copies/ml), constituting approximately 1/3 of the trial population, seemed to respond better to treatment with DRV/rtv compared with LPV/rtv. The same observation was not confirmed by stratification according to baseline CD4+ cells, although a similar tendency was observed as well. These results should be interpreted with caution because of the observed impact of the used non-

validated Kaletra regimen (once daily). This could lead to under-exposure to active drug concentrations in subjects taking the latter regimen. As the sub-group of once daily dosing in this stratification was high (>25%), the influence of sub-optimal exposure could be the underlying reason for the observed difference (and not, in fact, the better response to DRV/rtv). This is particularly true for patients with a high viral load (and very low CD4 cell counts), as they can be hypothesised to be more susceptible to periods of sub-optimal ARV treatment exposure. However, this did not influence the primary outcome of the trial since non-inferiority of DRV/rtv (800 mg/100 mg) q.d. to the approved LPV/rtv 400/100 mg b.i.d regimen in virological response was demonstrated.

- Discussion on clinical efficacy

The presented study with a recommended dose of 800/100 mg DRV/rtv q.d. using the new 400 mg Prezista tablets demonstrated non-inferiority of DRV/rtv to LPV/rtv at the predefined non-inferiority margin of 12% in treatment naïve patients.

Virologic response at 48 weeks in the DRV/rtv treatment group was 83.7% and 78.3% in the LPV/rtv group. The difference in virologic response (defined as the percentage of subjects with confirmed plasma viral load < 50 copies/ml) between DRV/rtv and LPV/rtv at 48 weeks was 5.3% (95% CI: -0.5% - 11.2%). This finding was supported by the results of different virological and immunological secondary endpoints. Also, sensitivity analyses demonstrated that this finding is robust and consistent for different populations and imputation methods.

In the DRV/rtv treatment group a lower percentage of virologic failures was observed compared with the LPV/rtv treatment group (9.9% vs. 14.2% respectively). This should be interpreted with caution because of the observed impact of the used non-validated Kaletra regimen (once daily), see above.

No development of PI resistance was observed during the 48 weeks under evaluation; in the virologic failures of the DRV/rtv group one developing NRTI RAM was identified, associated with a decreased susceptibility to FTC. In the LPV/rtv group two virologic failures with developing NRTI RAMs, and one subject with 2 additional developing PI RAMs at endpoint were identified.

These findings originate from the 48 week analyses from one open label randomised controlled trial in 689 HIV-1 infected, treatment naïve patients. The bias introduced by not blinding patients or investigators is not expected to have influenced the main outcome of the study. The findings of this trial are consistent with what was seen in treatment experienced patients in earlier studies.

Clinical safety

- Patient exposure

In the current trial, TMC114-C211, 343 persons have been exposed to DRV, of which all received the recommended dose of 800 mg DRV q.d. combined with 100 mg rtv q.d. By the cut-off date 13 June 2007 total patient years of exposure was 361.5 years; 306 subjects were followed for the full 48 weeks. The safety and tolerability findings from this trial, combined from what was already known from trials and experience in treatment-experienced patients, demonstrate a safety profile similar to that seen with other boosted PIs.

- Adverse events

In the DRV/rtv group 90.1% of subjects experienced ≥ 1 adverse event (AE). AEs at least possibly related to DRV/rtv, i.e. adverse drug reactions (ADRs) as assessed by the investigator, occurred in 50.1% of the subjects. In the LPV/rtv group 94.8% of subjects experienced at least 1 AE, of which 69.7% were considered at least possibly related.

The most common ADR was diarrhoea, which was reported in 23.0% of the subjects on DRV/rtv and in 46.5% of the subjects on LPV/rtv treatment. Other commonly reported ADRs were nausea (13.7%

in DRV/rtv, 25.1% in LPV/rtv), headache (6.1% in DRV/rtv, 7.8% in LPV/rtv), abdominal pain (3.5% and 6.6% respectively) and vomiting (3.2% and 7.8% respectively).

Treatment related events that were reported with a higher frequency on the DRV/rtv than LPV/rtv regimen were cardiac disorders and rash. Overall, the safety results of the present trial indicate favourable safety of DRV/rtv in treatment-naïve patients at the recommended dosage compared to LPV/rtv.

The frequencies of ADRs known to be associated with PIs (e.g. cardiac-related, rash, liver-related, lipid-related and glucose-related ADRs) were mostly comparable in the DRV/rtv group and the LPV/rtv group, with the exception of GI-related ADRs. A higher incidence of GI-related ADRs were observed in the LPV/rtv group (59.8%) compared with the DRV/rtv group (35.6%). Incidences of lipid-related and of liver-related ADRs were seen with a slightly higher frequency in the LPV/rtv group (9.8% and 4.3% respectively) compared with the DRV/rtv group (3.8% and 2.3% respectively). The overall incidence of rash related ADRs was not quite similar in both groups (5.5% in the DRV/rtv group vs. 2.9% in the LPV/rtv group). Slightly different incidences for the DRV/rtv and LPV/rtv groups were observed for cardiac-related (1.2% versus 0.3% respectively). The incidences of glucose-related ADRs were identical (0.6% versus 0.6% respectively).

- Serious adverse event/deaths/other significant events

Grade 3 or 4 AEs were reported in 18.7% and 21.7% of subjects in the DRV/rtv and LPV/rtv groups, respectively. The most common grade 3 or 4 AEs (preferred term) were hypertriglyceridaemia (0.9% and 2.3% with DRV/rtv and LPV/rtv, respectively), ALT increased (1.5% and 1.7%), AST increased (1.7% and 1.2%), blood amylase increased (1.2% and 0.9%), hypercholesterolemia (0.3% and 1.4%), and abdominal pain (0% and 1.2%). There was one report of Stevens Johnson syndrome in the DRV/rtv group, which was considered a very likely related serious adverse event (SAE) and reason for discontinuation of trial medication.

There was one death recorded in the DRV/rtv treatment group (diffuse large B-cell lymphoma) and 3 in the LPV/rtv treatment group (cardiorespiratory arrest, cerebrovascular accident, and disseminated tuberculosis). None were considered related to the treatment.

- Laboratory findings

Overall, the incidence of laboratory abnormalities was considered to be low. There were no relevant differences between the treatment groups in the incidence of grade 2-4 abnormalities for amylase (6.7% versus 5.0%), lipase (1.8% versus 1.7%), or creatinine (0.3% versus 0.6%). Grade 2-4 ALT abnormalities were observed in 8.5% of DRV/rtv subjects and 10.2% of LPV/rtv subjects, and Grade 2-4 AST abnormalities in 9.4% and 9.1% of subjects, respectively. Grade 2-4 increases in triglycerides were observed less frequently in the DRV/rtv group (2.9%) than in the LPV/rtv group (11.1%), as were grade 2-4 increases in total cholesterol (DRV/rtv: 12.9%, LPV/rtv: 22.7%).

The mean changes in Haematocrit, RBC and lymphocyte counts were comparable for the DRV/rtv and LPV/rtv treatment groups. A small mean increase in haemoglobin was observed for both treatment groups. For platelet count, a mean increase was observed for both treatment groups, which was slightly more pronounced for the LPV/rtv group than for the DRV/rtv group.

Graded haematology abnormalities of interest were related to neutrophil count: - 14.5% in the DRV/rtv group vs. 9.5% in the LPV/rtv group - and decreases in white blood cell (WBC) count - 7% in the DRV/rtv group vs. 3% in the LPV/rtv group. Haematocrit, RBC and lymphocyte counts below normal were observed in both treatment groups, with a higher incidence in the LPV/rtv group for haematocrit and RBC count (haematocrit: 10.3% and 19.8% with DRV/rtv and LPV/rtv, respectively; RBC, 20.3% and 26.5%) and a slightly higher incidence of lymphocyte count abnormalities in the DRV/rtv group (7.1% and 5.5% for DRV/rtv and LPV/rtv, respectively).

- Safety in special populations

There was a difference between treatment groups in the incidence of elevated liver enzymes in subjects co-infected with Hepatitis B or Hepatitis C. Grade 2-4 ALT elevations in subjects co-infected with Hepatitis B or Hepatitis C was 32.6% with DRV/rtv and 56.3% with LPV/rtv. A similar difference between the treatment groups was seen in the incidence of grade 2-4 AST elevations in these subjects; 23.3% with DRV/rtv and 45.8% with LPV/rtv.

- Cardiovascular safety & other safety parameters

There was no difference between the DRV/rtv treatment group and the LPV/rtv treatment group regarding change in vital signs parameters. A majority of patients experienced at least one vital sign abnormality, 70% of subjects in the DRV/rtv group and 69% in the LPV/rtv group. Common abnormalities relating to vital signs were abnormally high blood pressure values. AEs related to vital signs abnormalities were observed in 4.4% of the DRV/rtv and 4.1% of the LPV/rtv treated subjects. Most common was hypertension (3.5% and 2.3% respectively).

The change in ECG versus baseline was similarly small for both the DRV/rtv and LPV/rtv group. Both change versus baseline in PR interval as QRS were significantly different between the two treatment groups (Mann-Whitney U-test, $p<0.001$) respectively. A mean decrease in heart rate was observed, this was slightly larger for the LPV/rtv group (up to –5.4 bpm) than for the DRV/rtv group (up to -4.3 bpm). None of the differences relating to cardiovascular safety between the two treatment groups were considered to be clinically relevant.

The incidence of QTc abnormalities was comparable for the two treatment groups. In two subjects of the DRV/rtv group, increases in QTcF of >60 ms were seen. Increases of >60 ms in QTcB were seen in four subjects in the DRV/rtv group and 2 subjects in the LPV/rtv group respectively. No clinical events related to QTc prolongation were reported. Abnormally high values for PR interval were observed in 2.4% and 3.5%, and for QRS width in 0.6% and 0.3% of subjects in the DRV/rtv and LPV/rtv groups, respectively. Abnormally low heart rate values were observed in 4.8% and 5.9% of subjects in the DRV/rtv and LPV/rtv groups, respectively.

There were no clinically relevant changes over time in physical examination findings. Mean changes is anthropometric measurements were detected in both treatment groups.

- Discontinuation due to adverse events

The percentage of subjects who permanently discontinued treatment due to ≥ 1 AEs was lower in the DRV/rtv group (4.7%) than in the LPV/rtv group (7.8%).

- Safety data from other sources/trials

A pooled analysis of available safety data for PREZISTA was assessed in the context of pending type II variation procedure (EMEA/H/C/707/II/0015). This pooled analysis provided data on a larger population of HIV-1 infected subjects, including both ARV treatment-experienced and treatment-naïve subjects ranging from PI- and NNRT-experienced to PI- and NNRT-naïve. From this pooled safety analysis the following frequencies for the main ADR were detected: diarrhoea in 10.4%, nausea in 5.2%, headache in 5.2%, abdominal pain in 4.4% and rash in 4.1% of subjects.

- Discussion on clinical safety

Identified risks for DRV/rtv so far have included hepatotoxicity, hyperglycaemia, lipid abnormalities, viral resistance and drug interactions. The patient exposure is comparable to products of the same class at the same stage. The limited safety information after longer-term exposure is a point of concern that needs to be addressed in the Risk Management Plan (RMP). No new safety signals were identified in this treatment-naïve population.

Overall, the safety and tolerability findings from this trial, combined with the knowledge already gained from trials and experience in treatment-experienced patients demonstrate a safety profile similar to that seen with other boosted PIs.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The current version of the DDPS (3.0), dated 28 June 2007, was assessed during the first renewal of the conditional MA for the 300 mg strength (EMEA/H/C/707/R/08). As it was found to be appropriate, no issues needed to be followed up. Consequently, the CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The risk-management system currently in place for Prezista is described in the EU-RMP revision 7.0 issued 31 July 2008, submitted on 26 August 2008 together with PSUR 3.

The safety data of darunavir/ritonavir treatment in treatment naïve patients is still fairly limited. In the Risk Management Plan (RMP) there are several ongoing trials and more data will become available. Based on this limited data the incidence and severity of the adverse events do not give cause for changes in the RMP, except for the rash-related adverse events.

Rash-related adverse events, including Stevens Johnson syndrome (SJS), are already an identified risk in the RMP. In the complete database there have been 4 case reports of SJS, of which 1 ‘very likely related’, 1 ‘doubtfully related’, and 2 ‘not or doubtfully related’. In study TMC114-C211, there was one additional report of SJS which was assessed as ‘very likely related’.

The MAH was consequently within this procedure requested to amend the RMP of DRV/rtv, section 2.2.1’ Important Identified Risks’ for all rash-related events that have occurred with DRV/rtv. It was to be recorded whether the patients concerned were naïve, highly pre-treated or less pre-treated. Cardiac events were already sufficiently included in the RMP.

The MAH amended the RMP according to the question of the CHMP to stratify the rash-related events by treatment experience of the patient.

Further updates in version 7.0 of the RMP:
New exposure data available from trials TMC114-C202, TMC114-C213 and TMC114-C215 (cut-off Week 144 analysis) and trials TMC125-C206 and TMC125-C216 (cut-off Week 48 analysis), led to the update of the exposures for adults.

Regarding the identified risk “hepatotoxicity no new data became available.

Section 3.1 of the RMP was updated to mention the addition of lipodystrophy (encompassing lipohypertrophy, lipoatrophy and lipodystrophy) as an ADR to the CCDS of May 2008.

Regarding the identified risks for drug interactions: this section was updated with the data on the interaction trial on maraviroc with DRV/rtv. Regarding the risks for drug-drug interaction, this section was updated with the updated class labelling wording on the interaction with rifampicin.

No specific Risk Minimisation Program was ongoing at the start of the period under review. Only routine risk minimisation activities were in place. Apart for the updates on the new paediatric data no changes were made to the existing Risk Minimisation Plan for both routine and specific activities.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality data presented within this extension application is considered satisfactory and support the addition of the 400 mg strength.

Efficacy

The presented study with a recommended dose of 800/100 mg DRV/rtv q.d. using the new 400 mg Prezista tablets demonstrated non-inferiority of DRV/rtv to LPV/rtv at the predefined non-inferiority margin of 12% in treatment naïve HIV infected patients.

Virologic response at 48 weeks in the DRV/rtv treatment group was 83.7% and 78.3% in the LPV/rtv group. The difference in virologic response (defined as the percentage of subjects with confirmed plasma viral load < 50 copies/ml) between DRV/rtv and LPV/rtv at 48 weeks was 5.3% (95% CI: -0.5% - 11.2%). This finding was supported by the results of different virological and immunological secondary endpoints. Also, sensitivity analyses demonstrated that this finding is robust and consistent for different populations and imputation methods.

In the DRV/rtv treatment group a lower percentage of virologic failures was observed compared with the LPV/rtv treatment group (9.9% vs. 14.2% respectively). This should be interpreted with caution because of the observed impact of the used non-validated Kaletra regimen (once daily). The influence of sub-optimal exposure could be the underlying reason for the observed difference in response and failure (and not, in fact, the better response to DRV/rtv). This is particularly true for patients with a high viral load (and very low CD4 cell counts), as they can be hypothesised to be more susceptible to periods of sub-optimal ARV treatment exposure. However, this did not influence the primary outcome of the trial since non-inferiority of DRV/rtv (800 mg/100 mg) q.d. to the approved LPV/rtv 400/100mg b.i.d regimen in virological response was demonstrated.

No development of PI resistance was observed during the 48 weeks under evaluation; in the virologic failures of the DRV/rtv group one developing NRTI RAM was identified, associated with a decreased susceptibility to FTC. In the LPV/rtv group two virologic failures with developing NRTI RAMs, and one subject with 2 additional developing PI RAMs at endpoint were identified.

These findings originate from the 48 week analyses from one open label randomised controlled trial in 689 HIV-1 infected, treatment naïve patients. The bias introduced by not blinding patients or investigators is not expected to have influenced the main outcome of the study. The findings of this trial are consistent with what was seen in treatment experienced patients in earlier studies.

Safety

Identified risks for DRV/rtv so far have included hepatotoxicity, hyperglycaemia, lipid abnormalities, viral resistance and drug interactions. The patient exposure is comparable to products of the same class at the same stage. The limited safety information after longer-term exposure is a point of concern that needs to be addressed in the Risk Management Plan (RMP). No new safety signals were identified in this treatment-naïve population.

Overall, the safety and tolerability findings from this trial, combined with the knowledge already gained from trials and experience in treatment-experienced patients demonstrate a safety profile similar to that seen with other boosted PIs.

Benefit Risk assessment

Currently there is 48 week data available on efficacy, safety and tolerability of 800/100 mg DRV/rtv q.d. in treatment naïve patients. The virologic response of DRV/rtv has been demonstrated to be non-inferior compared with LPV/rtv at 48 weeks in the treatment of ART naïve HIV-1 infected patients,

which is considered to be a sufficient demonstration of efficacy for use in this patient group. The safety profile of DRV/rtv is favourable and consistent with data from the renewal application for the ART-experienced patients. In the presented data no concerns have been identified regarding the development of resistance at the recommended dosage of Prezista in the ART-naïve patient population. To assess the long term safety and resistance profile of DRV/rtv in ART naïve patients 96 week data will be provided. As committed, the company will submit the 96-week clinical study report in compliance with follow up measure FU2 024.1.

However, as the addition of the new treatment population of naïve patients is limited to only the 400 mg strength, the CHMP does not consider the broad indication of "HIV-infected adults" to be adequate, as the population of treatment experienced patients falls within another dosing regimen (DRV/rtv 600/100 mg b.i.d.) that cannot be made up with the applied for strength of 400 mg.

The final agreed wording for the indication is as follows:

"Prezista 400 mg, co administered with low-dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV 1) infection in Anti Retroviral (ARV) treatment -naïve adults."

In conclusion, the overall benefit-risk balance is considered to be positive for the 400 mg new tablets of PREZISTA at the recommended dosage for the limited indication of ART treatment naïve HIV-1 infected patients.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Prezista 400 mg, co administered with 100 mg ritonavir in combination with other antiretroviral medicinal products in the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral treatment naïve adults was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP reviewed the data submitted by the MAH taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and did not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see Attachment).

ATTACHMENT

CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 20 November 2008

1. Introduction

The MAH Janssen-Cilag International NV submitted on 6 March 2008 an extension application for a Marketing Authorisation to the European Medicines Agency (EMEA) for Prezista 400 mg Film-coated tablet, through the centralised procedure falling within the Article 2(a) and Annex II (point 2, intend iii) of the Commission Regulation (EC) No 1085/2003.

With the new strength the MAH also applied for a new indication adding treatment naïve patients to the existing population of antiretroviral experienced HIV-infected adults, treated with a darunavir/ritonavir 600/100mg twice daily regimen. The regimen for treatment naïve patients is darunavir/ritonavir 800/100mg once daily, therefore specific to the new strength of 400mg only.

The new indication was based on Week 48 analyses of plasma HIV RNA levels and CD4+ cell counts from one open-label controlled trial (TMC114-211, "ARTEMIS") in treatment naïve patients. Trial TMC114-C211 was a confirmatory trial that aimed at a comparison between darunavir/ritonavir 800/100 mg once daily and lopinavir/ritonavir 400/100 mg twice daily or 800/200 mg once daily, both in combination with a fixed background regimen of tenofovir disoproxil fumarate and emtricitabine. Lopinavir/ritonavir was chosen as comparator because it represents a recommended treatment option for the initial therapy of established HIV infection.

The data from this trial demonstrated robust and sustained virologic and immunologic benefits of darunavir/ritonavir 800/100 mg once daily together with the fixed background regimen over 48 weeks in treatment-naïve HIV-1 infected patients. In addition, darunavir/ritonavir 800/100 mg once daily was proven non-inferior to both dose regimens of lopinavir/ritonavir. The proof of the efficacy and an overview of the safety/tolerability profile of darunavir/ritonavir in treatment-naïve subjects was derived from the 48-week data from 689 subjects (343 on darunavir/ritonavir and 346 on lopinavir/ritonavir, who reached all 48 weeks of treatment or discontinued earlier) enrolled in trial TMC114-C211. Comprehensive data on virologic failure and resistance patterns were available. According to the CPMP/EWP/633/02 guideline, the primary endpoint to establish non-inferiority of darunavir/ritonavir versus lopinavir/ritonavir in trial TMC114-C211 was 48 weeks. Long-term safety data (96 week) were not included in this application.

With submission of this line extension application of the new strength together with its new indication in treatment naïve patients the MAH also applied for an additional one year marketing protection period in accordance with Article 14(11) of Regulation (EC) No 726/2004. The MAH claimed that taken together, the efficacy data observed with darunavir/ritonavir 800/100 q.d. support that darunavir brings a significant clinical benefit in comparison with existing standard of care in the HIV-1-infected treatment-naïve patient population.

2. Justification of significant clinical benefit as presented by the MAH

Significant clinical benefit based on improved efficacy
The Week-48 primary efficacy analysis of trial TMC114-C211 demonstrated that darunavir/ritonavir 800/100 mg q.d. in combination with a fixed background regimen of tenofovir and emtricitabine is an effective therapy in treatment-naïve, HIV-1-infected subjects. Non-inferiority in virologic response compared to treatment with a standard of care (lopinavir/ritonavir 800/200 mg daily) was shown. The efficacy of once-daily darunavir/ritonavir was not compromised, even in subjects who are considered the most difficult to treat, such as those with a high baseline viral load or low CD4+ cell count, and those with suboptimal levels of adherence to antiretroviral treatment. In contrast, lopinavir/ritonavir subjects with high baseline viral loads had significantly lower responses than those observed with darunavir/ritonavir and there was a trend towards lower response in those with low CD4+ cell counts and suboptimal adherence.

The greater virologic response with darunavir/ritonavir 800/100 mg q.d. versus a standard of care in subjects with high viral loads or the higher degree of virologic efficacy observed in those with low CD4+ cell counts (< 200 CD4+ cells/mm3) is particularly relevant, given the face of the HIV/AIDS

epidemic in the industrialised world nowadays. A significant proportion (up to 40% in certain countries) of treatment-naïve HIV-infected subjects currently living in the Western World only seek care when they have already reached a more advanced virologic and/or immunological stage of the disease. As well as being at higher risk of developing clinical HIV disease progression and short-term HIV-related death and therefore putting higher demands on clinical resources, these "late presenters" also appear to be less likely to have a sustained virologic response with the currently available antiretroviral therapies compared to those seeking care sooner in the course of HIV infection, although this seems to have improved somewhat in recent years.

Long-term adherence to antiretroviral treatment is a well-acknowledged challenge. The forgiving pharmacokinetics of darunavir as well as the MASRI results from trial TMC114-C211 suggests that darunavir is likely to provide benefits in this respect. Finally, genotyping and viral subtype determination establish the broad activity of darunavir/ritonavir q.d. against HIV-1, whereas the absence of development of PI resistance upon virologic failure with darunavir/ritonavir is consistent with what has previously been described with other boosted PI regimens in treatment-naïve subjects.

Taken together, the efficacy data observed with darunavir/ritonavir 800/100 q.d. support that darunavir brings a significant clinical benefit in comparison with the existing standard of care in the HIV-1-infected treatment-naïve patient population. The once-daily dose regimen of darunavir is likely to help curtail the challenges of long-term adherence and, therefore, in addition may lead to improved durability of first-line therapy.

Significant clinical benefit based on improved safety
The safety observations for the Week-48 analysis of trial TMC114-C211 are consistent with the known overall safety profile for darunavir/ritonavir and confirm its good safety and tolerability in treatment-naïve subjects. No new safety signals were observed in this trial versus previous data. Darunavir/ritonavir 800/100 mg q.d. is generally well tolerated with a more favourable overall tolerability profile compared with a standard of care (lopinavir/ritonavir, 800/200 mg total daily dose) in treatment naïve HIV-1-infected subjects. Discontinuations due to AEs are lower with darunavir/ritonavir (4.7%) than with lopinavir/ritonavir (7.8%).

Darunavir/ritonavir q.d. is associated with a lower incidence of gastrointestinal symptoms, most notable for diarrhoea and vomiting, compared to lopinavir/ritonavir. Gastrointestinal symptoms can be very disturbing for patients. Yet, these symptoms are among the most frequent AEs reported with antiretroviral therapy and are a particular problem with most of the currently available PIs. Gastrointestinal symptoms are also the most common driver of tolerability-related premature discontinuation of current (PI-based) HAART regimens and are a major barrier to optimal treatment adherence and thus, the long-term outcome of HAART. Although gastrointestinal AEs often abate over 4 to 6 weeks of therapy, some patients continue to experience symptoms over time. Controlled trials in treatment-experienced HIV-infected subjects have indicated that darunavir/ritonavir has improved gastrointestinal tolerability compared to other PIs, mainly as a result of a lower incidence and duration of diarrhoea. As diarrhoea can occur in up to 50% of subjects treated with PIs and significantly affects patients' emotional and physical well-being and quality of life, this lower incidence of diarrhoea represents a significant benefit.

Darunavir/ritonavir q.d. is also associated with a lower incidence of lipid abnormalities compared to lopinavir/ritonavir. Although lipid abnormalities can often be successfully treated with lipid-lowering agents, reducing the risk for lipid abnormalities by prescribing agents with a better tolerability profile in this respect may potentially reduce long-term cardiovascular risk, save concomitant medication cost, and prevent patients from being exposed to potential drug-drug interactions and resulting toxicities.

Moreover, daily use of 100 mg instead of 200 mg of ritonavir – a drug that appears to be associated with a higher probability of developing lipid abnormalities – constitutes an improvement of the q.d. dosing regimen of darunavir over the current PI standard of care, with a reduced frequency and severity of metabolic abnormalities.

Finally, a recent comparative trial of lopinavir versus efavirenz (the most preferred first-line antiretroviral treatment) showed that body changes occurred less frequently with lopinavir than with efavirenz. Darunavir/ritonavir appears to have limited impact with regard to body changes, as to date no early signal for such changes has been observed from anthropometric measures in clinical trials. Also in trial TMC114-C211, no clinically relevant differences between darunavir/ritonavir and lopinavir/ritonavir were seen for anthropometric measurements.

Significant clinical benefit based on major contribution to patient care
There has been a general trend for HIV treatment simplification through a decrease of pill burden and a lowering of dosing frequency. In this application, darunavir/ritonavir 800/100 mg q.d., in combination with an optimised background antiretroviral regimen, was proposed as the recommended dosing regimen for PI treatment-naïve (including antiretroviral treatment-naïve) adult HIV-1-infected subjects.

In addition to once-daily administration, darunavir/ritonavir has a low pill burden (2 x 400 mg tablet + 1 x 100 mg ritonavir per day). Based on the recommended doses as per Product Information, this is the lowest pill burden compared to the PI regimens that are currently approved for use in treatment-naïve subjects.

Therapies with once-daily dosing and a minimal number of pills are important for treatment naïve HIV-infected subjects, as these subjects are being introduced to chronic, lifelong therapy. Moreover, drug-related factors such as pill burden, dosing frequency, and acute tolerability and safety, have been identified as important predictors of treatment adherence in HIV-1-infected subjects. Better adherence may also prevent virologic failure, ensuing mutations and development of resistance. Data from a recent randomised trial in treatment-naïve subjects indicated that differential adherence – defined as any difference in self-reported level of adherence to individual antiretroviral agents at the same time point – was associated with an increased risk of initial virologic failure and initial virologic failure with antiretroviral resistance. In addition, it has been suggested that interventions to improve treatment adherence are a highly cost-effective use of resources.

Since medication regimens for HIV-infected subjects are frequently complex and rigorous, any improvement in dosing convenience and in safety and tolerability would be a welcome addition to the armamentarium of antiretroviral therapies. The once-daily dosing, the low pill burden and the forgiving pharmacokinetics of darunavir/ritonavir 800/100 mg q.d. bring more convenience to the patient and may help curtail the challenges of long-term adherence. The favourable tolerability and safety profile compared to the standard of care may lead to improved quality of life.

3. Assessment of the MAH's justification of significant clinical benefit

Significant clinical benefit based on improved efficacy
Regarding the argumentation from the MAH in relation to the efficacy claim, the CHMP concluded that the current data provided have shown that a regimen of darunavir/ritonavir is as effective as lopinavir/ritonavir in treatment naïve patients. However, the CHMP found that the clinical efficacy is not significantly improved when compared to the latter. This was clearly established in the outcome on the primary endpoint of the study comparing darunavir/ritonavir with lopinavir/ritonavir (ARTEMIS), in which non-inferiority was proven. Superiority, however, was not shown. Therefore, the CHMP concluded that whilst the benefit risk balance in the new indication for the new strength of Prezista is positive (therefore concluding in a positive opinion of the Committee for the extension application), the lack of proof of superiority in the submitted trial does not support the claim for a significant clinical benefit based on improved efficacy.

Regarding the claimed benefit in the subgroup of patients with a high viral load at baseline, the CHMP did not consider it proven that the observed higher response in those patients (approximately 1/3 of the total study population) was transferable into a clinical benefit: it is debatable whether the trial was robust enough to make such claims. The same applies for the observed trend in patients with a low CD4+ cell count at baseline. Furthermore, the CHMP was of the opinion that these differences might

be driven by the use of a non-validated once-daily lopinavir/ritonavir regimen. The influence of sub-optimal exposure could be the underlying reason for the observed differences in response and failure (and not, in fact, the better response to darunavir/ritonavir treatment). Finally, the CHMP was of the opinion that the influence of regional differences in response rates remains unclear with respect to the observed difference in these subgroups.

Additionally, comparative data versus other treatments were not provided by the MAH therefore hampering the CHMP's conclusions to be drawn in relation to a significant clinical benefit in comparison with other existing therapies.

Finally, regarding the MAH's argumentation towards a better long-term adherence, the CHMP was of the opinion that such a conclusion is mainly theoretical and indeed premature as it is based only on MASRI questionnaires in a single trial at Week 48. In addition to the relatively short observation period as presented within the ARTEMIS trial, the CHMP also considered that the number of patients enrolled is rather small, not allowing such a generalised conclusion. As a matter of fact, any claimed efficacy benefit based on long term adherence would need to be put into perspective with long term comparisons against the whole available treatment arsenal in the target population.

Significant clinical benefit based on improved safety
The CHMP was of the opinion that the claimed clinical relevant advantage regarding safety in the new target indication has not been conclusively shown with the provided ARTEMIS data. Whilst it is acknowledged that in comparison with lopinavir/ritonavir certain complications like GI side effects and lipid abnormalities were less frequently observed (at least in severity), the described effects on patients, e.g. treatment discontinuation, are not convincingly demonstrated since it can be debated whether the relatively small clinical trial is suitable to draw such conclusions on the clinical benefit in regards to safety.

Generally, the CHMP considered that a comparison against a single medication with respect to a specific type of adverse event as presented by the MAH is inconclusive. In order to understand whether the safety profile of darunavir/ritonavir in the target population is more benign than existing therapies, a full comparison with the whole repertoire for treatment of naïve patients would be necessary.

Significant clinical benefit based on major contribution to patient care
Finally, the argument of patient advantage based on the once-daily dosing regimen was not supported by the CHMP as there are other antiretroviral therapies in the target population of treatment naïve patients, which are dosed once daily. In addition, a comparison to lopinavir/ritonavir shows that the pill burden per day for darunavir/ritonavir is in fact higher (3 instead of 2 tablets per day) in treatment naïve patients.

4. CHMP Conclusion

Generally, the CHMP considered that the development of the Prezista dossier is not different from what would be expected for this type of product: initial authorisation for a limited patient population followed by a step wise approach for inclusion of a broader population.

The CHMP concluded that the efficacy and safety results of the ARTEMIS trial, together with the quality data provided, supported a positive benefit risk balance for the extension application for Prezista 400mg in treatment naïve patients. However, the lack of proof of superior efficacy results in the submitted trial did not support the claim for a significant efficacy benefit. Furthermore, the CHMP considered the safety profile of darunavir/ritonavir not to be significantly better. Finally, the CHMP judged the provided justification on improved patient care to not be sufficiently substantiated.

Overall, in the absence of significant clinical benefit based on improved efficacy, safety and contribution to patient care, in comparison both to the comparator lopinavir/ritonavir as well as other antiretroviral medicines indicated for treatment naïve patients, the CHMP considered that the

justification for an additional year of marketing protection was insufficient. Therefore, the CHMP did not support the MAH's justification for an additional year of marketing protection based on the new therapeutic indication for Prezista in treatment naïve patients.

5. Outcome

The CHMP reviewed the data submitted by the MAH taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and did not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.