15 March 2012
EMA/100380/2013
Committee for Medicinal Products for Human Use (CHMP)

Prezista

(darunavir)

Procedure No. EMEA/H/C/000707/P46/063

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

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Rapporteur's Final Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended Study TMC114-C212

Darunavir (Prezista)

EMEA/H/C/707

Marketing Authorisation Holder: Janssen-Cilag International N.V.

Rapporteur:	Dr. Barbara van Zwieten-Boot
Start of the procedure (day 0):	16 October 2011
Date of this report:	27 February 2012
Deadline for CMS's comments:	5 March 2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Prezista
INN (or common name) of the active substance(s):	Darunavir
MAH:	Janssen-Cilag International N.V.
Currently approved Indication(s)	PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. PREZISTA 75, 150 mg, 300 mg and 600 mg tablets may be used to provide suitable dose regimens: ● For the treatment of HIV-1 infection in antiretroviral treatment (ART) experienced adult patients, including those that have been highly pre-treated. ● For the treatment of HIV-1 infection in ART-experienced children and adolescents from the age of 6 years and at least 20 kg body weight.
Pharmaco-therapeutic group (ATC Code):	J05AE10
Pharmaceutical form(s) and strength(s):	Film-coated tablets 75 mg, 150 mg, 300 mg and 600 mg

1. RECOMMENDATION

After the review of the 96 weeks data on safety and efficacy from **paediatric trial TMC114-C212** the rapporteur required clarification of various outstanding questions. These issues, related to final clarification of denominators or explanation of possible associations between AEs, have now been sufficiently addressed by the MAH. The conclusion of the MAH that "*a revision of the currently approved SmPC, which contains the results from the TMC114-C212 Week-48 analysis, is not warranted"* is supported.

No new safety signals have emerged after 96 weeks of evaluation of the selected group of adolescents that was included in the extension period after the initial 48 weeks of study TMC114-C212 for PREZISTA.

The MAH's responses to the Request for Supplementary Information are summarized and assessed in section 4 of this AR.

2. Introduction

On 27 September 2011, the MAH submitted the final analysis of the completed paediatric study TMC114-C212 for PREZISTA, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

TMC114-C212 is part of a clinical development program. The 24 weeks data of TMC114- C212 was the initial scope of application EMEA/H/C/000707/X020, submitted to EMA June 27th 2008. 48 weeks data have been submitted in the Response to Questions of this same application, submitted to EMA Feb 18th 2009.

The MAH stated that the data submitted do not influence the benefit-risk balance for PREZISTA and therefore do not require to take further regulatory action on the marketing authorisation for PREZISTA.

Based on assessment of the submitted data, a Request for Supplementary Information was issued in November 2011. The MAH submitted a response to the rapporteur's questions on 17 January 2012.

2.1 Information on the pharmaceutical formulation used in the study

Darunavir (DRV, PREZISTA) is an inhibitor of the dimerization and catalytic activity of the human immunodeficiency virus (HIV-1) protease. The following indication for the use of DRV in pediatric patients is currently approved:

PREZISTA 75, 150, 300 and 600 mg, co-administered with low-dose ritonavir (rtv) is indicated in combination with other antiretroviral (ARV) medicinal products for the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced children and adolescents from the age of 6 years and at least 20 kg body weight.

Posology:

- for subjects ≥ 20 to < 30 kg: 375/50 mg twice daily (b.i.d.) DRV/rtv

- for subjects ≥ 30 to < 40 kg: 450/60 mg b.i.d. DRV/rtv

- for subjects ≥ 40 to < 50 kg: 600/100 mg b.i.d. DRV/rtv

The current Summary of Product Characteristics (SmPC) includes the 48-week efficacy and safety data of DRV/rtv in combination with other ARV medicinal products from Phase II study TMC114-C212 (or DELPHI) in ART-experienced pediatric subjects aged 6 to < 18 years and weighing ≥ 20 kg.

The MAH provided the final results of study TMC114-C212 as collected at the last patient visit on: March 30, 2011 with a focus on long-term safety data.

No new clinically relevant safety concerns were identified compared to the known safety profile of DRV/rtv in pediatric subjects.

2.2 Information on study TMC114-C212

Study TMC114-C212 was a Phase II study, evaluating pharmacokinetics, short-term safety, tolerability and antiviral activity to support dose recommendations of DRV/rtv in combination with other ARV medicinal products in ART-experienced HIV-1 infected pediatric subjects aged 6 to < 18 years and weighing ≥ 20 kg.

In addition, the efficacy, long-term safety and tolerability of DRV/rtv in combination with other ARV medicinal products were evaluated over a 48-week treatment period. Subjects ≤ 18 years of age at the moment of reaching the Week-48 visit, and living in a country where pediatric use of DRV was not yet part of the local prescribing information, had the opportunity to roll over to an optional extension phase of the study where they received DRV/rtv until the subject became 18 years and DRV was available through the local Health Care Systems or until DRV was registered for use in pediatric subjects.

The recommended dose of DRV/rtv in ART-experienced HIV-1 infected pediatric subjects aged 6 to < 18 years and weighing ≥ 20 kg was determined during Part I of the study. Based on short-term safety, tolerability, antiviral activity, and pharmacokinetic/pharmacodynamic data of the planned Week-2 analysis, the following dosages were recommended:

- for subjects ≥ 20 to < 30 kg: 375/50 mg twice daily (b.i.d.) DRV/rtv

- for subjects ≥ 30 to < 40 kg: 450/60 mg b.i.d. DRV/rtv

- for subjects ≥ 40 to < 50 kg: 600/100 mg b.i.d. DRV/rtv

Throughout the study, all subjects received DRV/rtv in combination with an optimized background regimen that included at least 2 ARV medicinal products, i.e., a combination of nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI[s]) and/or allowed nonnucleoside reverse transcriptase inhibitor (NNRTI) and/or a fusion inhibitor (enfuvirtide). The dosing schedule of the ARV medicinal products in the optimized background regimen as described in the package inserts had to be respected.

Long-term safety, tolerability and efficacy of these selected DRV/rtv doses were evaluated up to 48 weeks in Part II of the study. The primary analysis was performed at Week 24, and an update of the analysis was performed at Week 48. The Week-48 results were comparable to the Week-24 results, and the analyses supported the use of the selected doses of DRV/rtv in combination with other ARV medicinal products in ART-experienced HIV-1 infected subjects aged between 6 and < 18 years and weighing ≥ 20 kg.

2.3 Final analysis

The objective of the final analysis of the study was to update the Week-48 analysis with all data collected during the extension period up to March 30 2011.

The final analysis was conducted when:

- all recruited subjects had completed the study,
- had switched to commercially available DRV,
- rolled over to the pediatric continued-access study TMC114-TiDP29-C232, or
- had discontinued DRV/rtv treatment.

The final analysis included an analysis of subject and treatment information (subject disposition and study completion, concomitant therapies, protocol deviations, treatment compliance, extent of exposure), safety (adverse events including deaths, laboratory safety, physical examination, Tanner scale, anthropometric parameters), efficacy (viral load, immunology), and resistance determinations.

Demographic parameters, baseline disease characteristics, electrocardiograms, pharmacokinetics, and pharmacokinetic/pharmacodynamic parameters were not analyzed because no or few new data were available compared with the Week-48 analysis.

The data collected during the extension phase should be carefully interpreted, because:

- the extension phase was limited to a subset of subjects (living in a region where DRV was not registered for pediatric use);
- background therapy was allowed to change during the extension phase at any time;
- subjects had to stop treatment at the time when DRV became available for use through Health Care Systems or when registered for use in pediatric subjects in the region the subject was living in;
- no pre-specified objectives or time points of interest were defined for the extension phase.
- It was a limited sample size, that further decreased during the extension period.

3. SCIENTIFIC DISCUSSION

3.1 Completion/Withdrawal Information

A total of 80 subjects participated in the study, at the time of the cut-off for the Week-48 analyses, 75 subjects (93.8%) had reached 48 weeks of treatment.

Fourteen (17.5%) of the 80 subjects did not continue treatment in the extension phase:

- 5 subjects had completed 48 weeks of treatment and did not continue in the extension phase
- 9 subjects had discontinued prematurely.

Therefore, 66 (82.5%) subjects continued treatment in the extension phase. At study end, the majority of subjects had switched to commercially available DRV (25 subjects, 31.2%) or had rolled over to the continued-access study TMC114-TiDP29-C232 (19 subjects, 23.8%).

In the final analysis,

- 58 (72.5%) subjects were treated for at least 96 weeks,
- 32 (40.0%) for at least 144 weeks,
- 23 (28.8%) for at least 192 weeks, and
- 15 (18.8%) for 216 weeks.

Of the entire intent-to-treat (ITT) study population in total 31 (38.8%) subjects discontinued treatment due to:

- noncompliance (12 subjects, 15.0%),
- adverse events or HIV-related events (5 subjects, 6.3%),
- reaching a virologic endpoint (5 subjects, 6.3%),
- withdrawal of consent (1 subject, 1.3%), or other reasons (8 subjects, 10.0%).

3.2 Study results

The final analysis of study TMC114-C212 in pediatric treatment-experienced HIV-infected subjects (6-<18 years) was provided by the MAH. These children and adolescents were prescribed a weight-based regimen that was reviewed and approved in earlier assessment reports. In general no new findings were reported that could compromise the previously concluded positive risk-benefit balance following analysis of the 48 week data.

From the initial cohort of 80 children 6-<18 years only 66 entered the extension phase and 58 completed the 96 weeks study observation.

With regard to efficacy, 35 subjects from the initial cohort had viral load < 50 copies/ml at week 96 (47%). The analysis of TMC114-C213 and TMC114-C202 in treatment experienced adults demonstrated similar efficacy rates.

Virologic failure was reported for 45 of the initial 80 subjects i.e. 56%. In the analysis of treatment-experienced adults in TMC114-C213 and TMC114-C202 at week 96 these rates were similar, as has been elucidated by the MAH.

Concerning resistance it was observed that in the available samples 9 from 25 virologic failures (36%) developed decreased susceptibility to DRV, but poor adherence to either DRV or OBT did not contribute significantly to these figures. No additional DRV RAMs were identified.

No new or relevant safety issues appeared in the period between 48 weeks and the time of the final analysis, because the 8 additional SAEs and also the 4 additional AEs that results in discontinuation were not considered to be related to DRV. These data on safety and tolerability support the findings as previously established in children at week 48, including improvement in development and growth.

The final data demonstrate that in this pediatric population, DRV/rtv dosed b.i.d. per body weight and in combination with other ARV medicinal products has a safety and efficacy profile comparable to that described in the Week-48 analysis and to that observed in HIV-1 infected ART-experienced adults. The previously reported positive benefit-risk ratio is not changed from week 48 until the date of the final analysis.

4. REQUEST FOR SUPPLEMENTARY INFORMATION

4.1 Rapporteur's assessment of MAH's responses to RSI

A summary of the MAH's responses to the rapporteur's questions, together with the assessor's comments are given below:

Question 1:

Concerning virologic response: was the total number 74 as mentioned in Table 18, 66 being the number of patients in the extension phase, or 58 being the number at least 96 weeks in the study?

The MAH's Response:

The total number of subjects considered to determine confirmed virologic response (ITT - TLOVR) for a given time point was calculated as: 'the number of ITT subjects' minus 'the number of subjects being censored out before the considered time point'. Subjects were to be censored out if: 1) they completed the 48-week treatment phase, but did not participate in the extension phase, or 2) they discontinued the extension phase due to rollover (to the pediatric continued-access trial TMC114-C232), or due to switching to commercially available DRV.

Hence, the denominator for time points in the extension phase was determined as follows:

- the number of ITT subjects was 80;
- 5 subjects who completed the Week-48 visit but who did not participate in the extension phase were censored out for all extension time points;
- 1 subject switched to commercial DRV use during the Week-60 time window, and was censored out for all assessment time points following that time window;
- all other subjects were included for all time points (up to the last available visit, i.e., Week 216)

Therefore, the denominator during the extension phase, up to and including the Week-60 visit was 75 (80 - 5 = 75), while for the extension visits following the Week-60 visit (as presented in Module 5.3.5.2/TMC114-C212-W48-CSR-add/Table 18), it was 74 (80 - 5 - 1 = 74).

Assessor's comment

Week 60 visit is not an endpoint in the study. The selection of subjects to continue or discontinue in the extension phase is partly investigator-driven and therefore the denominator of n=74 (at start), n=66 during the extension and n=58 at week 96 is not a reliable representation of the initial study population. The virologic endpoint is therefore hard to compare to other long term studies. However, since the virologic endpoint in this age group is only reported for the week 48 period in the SmPC, this issue is not relevant.

Issue solved.

Question 2:

No data are presented on these adherence parameters and virologic outcome including resistance.

The MAH's Response:

Adherence data based on the PENTA Questionnaire were collected during the extension phase, and analyzed and presented in the Clinical Study Report (CSR) Addendum reporting the TMC114-C212 final analysis (Module 5.3.5.2/TMC114-C212-W48-CSR-add/Section 2.4).

As no plasma concentration or pill count data were collected during the extension phase, no adherence based on these parameters could be determined.

There was no apparent relationship between virologic response (< 50 copies/mL, ITT - TLOVR) at endpoint and DRV/rtv adherence:

There was no apparent relationship between virologic response (< 50 copies/mL, ITT - TLOVR) at endpoint and OBR adherence:

- 19 out of 49 (38.8%) of adherent subjects achieved virologic response compared to 10 out of 31 (32.3%) nonadherent subjects.

Also the development of resistance (i.e., development of mutations and loss of phenotypic susceptibility to ARVs in the treatment regimen) appeared not to be associated with adherence:

no evidence of a clinically relevant relationship between DRV/rtv adherence and the development of PI RAMs ; DRV/rtv adherence and the development of DRV RAMs ; DRV/rtv adherence and loss of susceptibility to DRV ; OBR adherence and the development of NRTI mutations ; OBR adherence and loss of susceptibility to ≥ 1 NRTI in the OBR in virologic failures were recorded.

In conclusion, based on the PENTA Study Adherence Questionnaire, no correlation was observed between adherence to DRV/rtv or the OBR versus virologic outcome, and between adherence to DRV/rtv or the OBR versus resistance development in study TMC114-C212.

Assessor's comment
Adherence rates are only reported as obtained from questionnaires which is less robust as measurement of adherence using pill counts or PK parameters.

At least in this less robust method no association was demonstrated between non-adherence and virologic response; number of PI resistance associated mutations; number of DRV RA-mutations; number of NRTI RAMs; and phenotypic resistance.

Issue solved.

Question 3:

How could the total number of "never suppressed" diminish from Week 48 until the final analysis?

The MAH's Response:
Of the 32 subjects classified as 'never suppressed' in the Week-48 analysis, 26 subjects were still classified as 'never suppressed' in the final analysis, 3 subjects became 'rebounders' (i.e., after the Week-48 analysis, achieved but subsequently lost a confirmed plasma viral load < 50 copies/mL), and 3 subjects became 'late' responders (i.e., after the Week-48 analysis, achieved a plasma viral load < 50 copies/mL).

For this reason, the number of never suppressed subjects was 32 in the Week-48 analysis, versus 26 in the final analysis. (See also the response to Question 5 and Figure 1.)

Assessor's comment
The category 'never suppressed' was subject to additional modifications due to investigator-driven decisions. Since virologic response or virologic failure beyond the initial 48 weeks will not be reported for this age group in the SmPC, this issue is not relevant.

Issue solved

Question 4:

Virologic failure was reported for 45 of the initial 80 subjects, i.e. 56%. In the analysis of treatment-experienced adults in TMC114-C213 and TMC114-C202 at week 96 virologic failure was 29%. Can the MAH explain the increase in virologic failure?

The MAH's Response:

The MAH cannot confirm the number of 29% of virologic failures in the 96-weeks TMC114-C202 /TMC114-C213 pooled analysis.

In this analysis, when using a threshold of a decrease in plasma viral load of ≥ 1 log10 copies/mL from baseline (the primary efficacy parameter), 41 out of 131 (31.3%) subjects were categorized as virologic failures.

When using a threshold level of plasma viral load < 50 copies/mL (the primary efficacy parameter in TMC114-C212), 69 out of 131 (52.7%) subjects were virologic failures at Week 96 in the TMC114-C202 /TMC114-C213 pooled analysis. This is comparable to the rate for the same viral load threshold in the TMC114-C212 final analysis (45 out of 80 subjects, 56.3%).

Note that the confirmed virologic response rate (< 50 copies/mL, ITT - TLOVR) at Week 96 in the TMC114-C212 final analysis was also comparable to the rate observed in the Week-96 TMC114-C202 /TMC114-C213 pooled analysis:

- 35 out of 74 (47.3%) subjects in TMC114-C212;
- 51 out of 131 (38.9%) subjects treated with DRV/rtv 600/100 b.i.d. from study start in TMC114-C202 /TMC114-C213.

Based on the above, the MAH concludes that the findings on virologic failure or lack of virologic response in the final analysis of TMC114-C212 in treatment-experienced pediatric subjects between 6 and < 18 years are consistent with those of the Week-96 TMC114-C202 /TMC114-C213 pooled analysis in treatment-experienced adults.

However, as the mean exposure in the Week-96 TMC114-C202 / TMC114-C213 pooled analysis was substantially lower compared to that in the TMC114-C212 final analysis (104.7 versus 131.6 weeks), any comparisons between both analyses should be interpreted with caution.

Assessor's comment

As stated by the MAH the comparison between both analyses is difficult, since the extension period is subject to investigator-driven selection. Virologic failure rates appear similar.

Issue solved.

Question 5:

If 12 subjects experienced rebound virologic failure from Week 48 until the time of final analysis, how come only 6 virologic failures were reported?

The MAH's Response:

In the TMC114-C212 final analysis, 19 subjects experienced rebound compared to 7 subjects in the Week-48 analysis. The 19 rebounders in the final analysis include: the 7 subjects from the Week-48 analysis, 3 subjects who were classified as never suppressed in the Week-48 analysis but who became rebounders by the time of the final analysis (see also the response to Question 3),

and 9 additional subjects who experienced rebound from the Week-48 analysis to the time of final analysis.

In addition, from Week 48 until the time of final analysis, 3 subjects who were never suppressed at the time of the Week-48 analysis, achieved a virologic response (see also Question 3).

Consequently, there were in total 6 additional subjects who experienced virologic failure (rebound or never suppressed) in the final analysis compared to the Week-48 analysis.

A schematic overview of virologic failure outcomes for the Week-48 and final analyses is shown in Figure 1, including the numbers of subjects who switched categories between the 2 analyses.

Assessor's comment
The provision of data from patients subject to virologic failure is broken down to rebound or never suppressed. Since these data beyond week 48 will not be reported in the SmPC for this age group, these shifts in post-week 48 data will not change the results of week 48 for virologic response, rebounders and never suppressed.

Issue solved

Question 6:

It is unclear how much was INR increased and whether it could be related to use of DRV. Were the subjects that experienced an increase in INR also subjects that had an increase in transaminases?

The MAH's Response:
The grade 3 AE of increased INR occurred in 3 subjects (3.8%) in the final analysis (CRF ID

C212-0032, C212-0039, and C212-0069) compared to 1 subject (1.3%) in the Week-48 analysis (CRF ID C212-0032). The event was considered possibly related to DRV for Subject C212-0032, and not related to DRV for Subjects C212-0039 and C212-0069.

All observed grade 3 INR increased values in the TMC114-C212 final analysis, were not clinically significant findings, as the abnormalities were transient (occurring at only 1 time point) and isolated (no associated clinically relevant increase in transaminases), with no consistent pattern in the time to onset (Weeks 2, 96, 144), and none requiring modification of treatment.

Assessor's comment
No association was demonstrated between raised transaminases, as a possible manifestation of decrease of liver function, and increased INR values.

Issue solved.

Question 7:

There appears to be a discrepancy between the judgments on relation with triglycerides and use of DRV, since increase in triglycerides (i.e. hypertriglycideremia when crossing a prespecified cut off value) is a common adverse events according to the SmPC. The used criteria should be clarified.

The MAH's Response:
The relationship of DRV/rtv to the grade 1 AEs 'blood triglycerides increased' (very likely related) and 'hypertryglyceridemia' (not related) (each occurring in 1 subject, 1.3%), reflects the assessment of the investigator at the time of AE reporting.

However, the MAH acknowledges that an increase in triglycerides is a known adverse drug reaction with the use of DRV/rtv, as is appropriately described in the SmPC.

Assessor's comment
The drug-associated AE of hyperglyceridemia is included in the SmPC.

Issue solved.

4.2 Summary and Conclusions

Various questions were raised by the rapporteur on the interpretation of number in groups that continued in the extension phase. Because this group was not randomly selected the efficacy results should be interpreted with caution. As such these virologic results beyond week 48 will not be reported in the SmPC. The MAH has stated that these findings will not result in changes to the SmPC which is endorsed.

One concern was the poor adherence to DRV in adolescents. However, the findings that were reported in the reply by the MAH did not demonstrate any difference in virologic response or any serious resistance issues to appear during the study period because no increased PI RAMs, DRV RAMs, NRTI RAMs or phenotypic resistance were noticed when the two groups (adherent versus non-adherent) were compared. Unfortunately, these data probably are based on overestimation of adherence because these data are derived from questionnaires and not from pill counts. At least in this less robust analysis no difference in virologic outcome were seen.

Two safety concerns were raised. One about the possible association between increased transaminases due to DRV and increased INR, but the analysis did not reveal worrisome signals in this respect. In addition hypertriglyceridemia was noticed, but since this is already included in the SmPC, this issue is not of additional concern.

In conclusion, all questions have been sufficiently answered, without further concerns about efficacy or safety in the age group of study TMC114-C212 for PREZISTA.

5. RAPPORTEUR'S OVERALL CONCLUSION

The MAH has sufficiently answered the remaining questions related to the presented data, and no further changes to the SmPC are required.