European Medicines Agency

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ASSESSMENT REPORT FOR APTIVUS

International Nonproprietary Name:
Tipranavir

Procedure No. EMEA/H/C/000631/X/30

Marketing Authorisation Holder (MAH):
Boehringer Ingelheim International GmbH

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

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1. Introduction

Problem statement
In younger children, the use of liquid formulations may be necessary since they may be unable to swallow capsules or may need smaller doses than adults. There is also a need for liquid formulations in adults and older children, who cannot swallow solid formulations. Common complications of HIV infection, such as oesophageal or oral candidiasis or herpes simplex, can result in severe pain and make swallowing solids impossible. For these reasons, the MAH undertook the clinical development of Aptivus oral solution (OS), at the beginning of 2003.

As part of the initial marketing authorisation application (MAA) for Aptivus submitted on 3 November 2004, the company submitted bioavailability (BA) data on the oral solution and the capsules (Study 1182.45). Following review of the data, the CHMP concluded that the bioequivalence (BE) between the capsule and oral solution was not demonstrated. There was a need to substantiate the interchangeability of the capsule and the oral solution to enable proper dosing recommendations and to ensure adequate efficacy and safety of the OS before a MA for this pharmaceutical form could be granted. On 1 July 2005, the MAH withdrew the application for the OS. A marketing authorisation was granted only for TPV capsules on 25 October 2005.

In November 2006, the MAH submitted the additional relative BA and pharmacokinetic (PK) data on the OS requested by the CHMP (Study 1182.100, Follow-Up Measure FUM 022). These data were assessed by the CHMP in March 2007. The MAH submitted responses to the CHMP conclusions in October 2007.

In support of the present Annex II application, the MAH has provided data on the quality and the relative BA of the OS.

About the product
TPV is a non-peptidic protease inhibitor (PI) that has been developed for treatment-experienced patients who have HIV-1 strains with PI resistance associated mutations.

On 25 October 2005, Aptivus was authorised in the EU under exceptional circumstances for combination antiretroviral treatment of HIV-1 infected adult patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one PI. The recommended dose is 500 mg TPV, co-administered with 200 mg ritonavir (RTV, if used as booster =/r), twice daily (b.i.d.). In February 2008, following the 2nd annual reassessment, the CHMP recommended that the exceptional circumstances be lifted since all Specific Obligations had been fulfilled. Aptivus is currently available as 250 mg soft gelatin capsules (120 capsules in HDPE bottles).

The MAH has now submitted an application for an extension to the MA for Aptivus to add a new pharmaceutical form i.e. a 100 mg/ml oral solution. The medicinal product is packaged in a 100 ml amber glass bottle with a plastic child resistant closure. The bottle is fitted with a plastic adapter for use with the 5 ml oral dispenser (syringe) supplied separately in the package.

This new pharmaceutical form is intended for patients from 2 years of age. In parallel, the MAH has applied for an extension of the indication for the currently approved 250 mg capsules to include paediatric patients aged 2 years and older. This application is assessed within procedure EMEA/H/C/631/II/29.

The proposed therapeutic indication for Aptivus oral solution is: *"Aptivus, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated patients 2 years of age or older with virus resistant to multiple protease inhibitors."*

The proposed recommended dose for children (2-18 years), based on body surface area (BSA) is 375mg/m^2 TPV co-administered with 150 mg/m^2 RTV, b.i.d. The paediatric dose should not exceed the adult dose. TPV oral solution co-administered with low dose oral solution RTV should be taken with food, in line with the approved dosing recommendations for TPV capsules.

The development programme/Compliance with CHMP Guidance/Scientific Advice
The developed TPV OS was first intended for younger children who are unable to swallow the capsules and who need dose adjustment (smaller dose than adults). The OS is also intended for adults and older children unable to swallow the capsules.

As mentioned above, the BA of TPV OS was evaluated in two BE studies:

- a Phase I study (1182.45) to assess the relative BA of TPV from both capsule and OS formulations at 500 mg b.i.d., each co-administered with RTV 200 mg b.i.d (TPV/r 500/200).
- a Phase I study (1182.100) to assess the relative BA of TPV/r 500 mg/200 mg at steady state when TPV and RTV are administered as OS versus capsules in the fed and fasted state.

The design of the Study 1182.100 was not in line with the CHMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) as detailed below.
No formal scientific advice was given by the CHMP for Aptivus Oral Solution.

General comments on compliance with GMP, GLP, GCP
GMP compliance
Roxane Laboratories, Wilson Road Columbus, Ohio, USA will be in charge of the manufacture, packaging and QC testing of the Oral solution. Roxane Laboratories, Oak Street, Columbus, Ohio, USA is proposed as back up site for the QC testing. Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany will be responsible for batch release in the EEA. A copy of the manufacturing authorisation has been provided for the site located in the EU. The manufacturing site Boehringer Ingelheim Roxane Inc., Wilson Road, Columbus was inspected in March, 2007 by the German competent authority with respect to GMP compliance. The inspection report states a positive outcome of the inspection.

GLP compliance
Supportive non clinical data are derived from the dossier related to Aptivus 250 mg soft capsule, where GLP status of the studies was considered adequate to allow assessment of the pivotal studies.

GCP compliance
The MAH states that the studies relevant to this application were conducted in accordance with the principles of GCP.

2. Quality aspects

Introduction

Aptivus contains tipranavir as the active substance and it is presented in the form of 100 mg/ml oral solution. It is yellow, viscous clear liquid. Other ingredients present in the formulation include macrogol 400, propylene glycol, mono/diglycerides of caprylic/capric acid, vitamin E polyethylene glycol succinate, ascorbic acid, purified water, sucralose and flavouring agents buttermint and butter toffee.

The product is packed in glass amber bottle with two-piece child-resistant closure and is supplied with a clear polypropylene (PP) 5 ml graduated dispensing syringe, PP syringe cap and clear low-density polyethylene (LDPE) bottle-syringe adapter.

Drug substance

The same drug substance that has been approved for Aptivus 250 mg soft capsules has been used for development of the new oral solution pharmaceutical form, and is proposed to be used in commercial batches of tipranavir oral solution.

Drug Product

- Pharmaceutical Development

The aim of the development program was to formulate an oral solution for paediatric and adult patients who cannot swallow capsules.

Due to the poor water solubility of tipranavir (active substance) and due to the poor *in vivo* exposure of conventional tipranavir solid prototype formulations the development of an aqueous solution or a suspension was precluded. Therefore, a self-emulsifying drug delivery system (SEDDS) formulation, in which the drug substance is already dissolved, was chosen to overcome the dissolution rate limited absorption of tipranavir.

The following reasons have been considered during the development of the formulation:
- liquid dosage form was needed for paediatric and adult patients who have difficulty swallowing tipranavir capsules 250 mg. A suspension had been precluded due to the poor *in vivo* exposure of solid prototype formulations.
- emulsifier was needed to overcome the dissolution rate limited absorption of the drug substance in the aqueous environment of the gastrointestinal tract.

All excipients used in the formulation are widely used in commercial pharmaceutical dosage forms and/or as food additives. The oral solution is a SEDDS, in which tipranavir free acid form is solubilised. The selection of the excipients was based on the results from the formulation development.

A SEDDS formulation allows a high drug load in the dosage form, which is necessary as the daily dose is proposed to be up to 1000 mg/day.

The chosen oral formulation includes a lipid phase, a surfactant/emulsifier and other appropriate components to achieve satisfactory drug solubility, dispersibility, bioavailability and physical and chemical stability.

Macrogol 400 (polyethylene glycol 400) and propylene glycol were chosen as co-solvents in the SEDDS formulation due to the high solubility of tipranavir in both excipients. Capmul MCM was selected as the lipid phase since the mono/diglycerides exhibit better performance than triglycerides (Miglyol).

Vitamin E TPGS (D-alpha-tocopheryl polyethylene glycol 1000 succinate) was selected as surfactant on the basis of an initial screening study and was found to produce a self-emulsifying system at a lower level than the other surfactants.

Due to the known potential to oxidative decomposition of the drug substance an antioxidant was required in the formulation. Ascorbic acid has been chosen as the most effective with respect to the chemical stability of tipranavir when compared with other antioxidants (based on an antioxidant screening study in which different antioxidants were compared). Limits set at release and shelf-life take into account the observed decrease upon time and the minimum acceptable level for the antioxidant.

Based on the results of placebo formulations study evaluating taste masking properties and sweetening power, sucralose was selected as the preferred sweetener among other sweeteners, and Buttermint and Butter Toffee were selected as flavouring agents among other flavouring agents.

A dispersion test has been used as a development tool during formulation development to assess the excipient effect on the dispersion behaviour of this formulation. Experimental data were provided with respect to identification of optimal excipients ratios and robustness of the formulation and no changes were observed during the long term and accelerated stability studies.

Besides some transient solvates which mostly desolvate under the process drying conditions, there are two polymorphic forms of tipranavir, Form I and II. Only Form I has been used during development work and is the proposed commercial form of the drug substance. The physicochemical properties of both forms are comparable. Nevertheless, polymorphism is not regarded relevant, since tipranavir is completely dissolved in the oral solution. Neither Form I nor Form II will precipitate from the solution during storage since their solubility is significantly higher than the 100 mg/ml formulation concentration.

The physical stability is limited by a drug substance-excipient interaction between tipranavir and Capmul MCM leading to the formation of a solvate of tipranavir with 1,3-dioctanoylglycerol (1,3-DOG solvate). This 1,3-DOG solvate is less soluble in the solution formulation than tipranavir itself. The solvate appears as a crystalline precipitate (at the bottom of the bottle), and was first observed in development samples stored under low temperature conditions (4°C and 15ºC). Results from stability studies performed on development batches stored at 4°C and 15°C have shown that the rate of formation of the 1,3-DOG solvate is accelerated at low temperatures. Therefore the storage statement for the product specifically warns against storing the product at either refrigerated or freezing conditions, or below 15°C. Once formed, the 1,3- DOG solvate crystals cannot be re-dissolved simply by shaking. However, small amounts of the solvate can be re-dissolved by warming to approximately 60ºC with no loss in product potency or increase in degradation products.

Due to the occurrence of the tipranavir 1,3-DOG solvate during storage and missing information about the toxicological relevance of this precipitate, additional data on the tipranavir 1,3-DOG solvate was necessary in order to evaluate the stability of the drug product, its shelf-life, storage warnings and in-use shelf life. The applicant provided structural data for the tipranavir 1,3-DOG solvate showing that it is a non-covalent association of tipranavir and 1,3-DOG in a molecular ration 4:1. Therefore, the toxicity of the solvate will be comparable to that of tipranavir and 1,3-dioctanoylglycerol taken separately. As the toxicity of the solvate was not a concern, and since it does not significantly affect tipranavir assay over the shelf life of the product, the issue was considered solved.

In addition the control of the physical quality of the solution is performed at release by means of microscopic test and at end of shelf-life by means of visual test. Moreover patients are instructed (section 6.6 of the SPC) to inspect the bottle and to return the product for replacement if there is more than a paper-thin layer of crystals in the bottle or any uncertainty as to the amount observed. Warming the product is not recommended to dissolve the crystalline precipitate as this is not considered necessary under the above described control scheme.

The formulation composition of the tipranavir 100 mg/ml oral solution used in the clinical batches is identical to the proposed commercial product.

During the development program the accuracy and precision of the dosing syringe (5 ml) was investigated over a range from 0.8 ml to 5 ml, corresponding to four different dose volumes of solution that mimic potential dosing plans for patients (0.8 ml, 1.2 ml, 2.5 ml and 5 ml). Variability among syringes was determined by using additional three syringes to dispense the same four volumes (one syringe per dose volume). The experimental data demonstrate the repeatability, intermediate precision and accuracy of the dose volumes delivered using the 5 ml dosing syringe.

- Manufacture of the Product

The manufacturing process of tipranavir 100 mg/ml oral solution follows standard manufacturing procedures for liquid solution products. The manufacturing process includes mixing steps of tipranavir drug substance and excipients to form a clear bulk solution and to filter the bulk solution to remove extraneous particles. Optimisation studies were performed to select the optimal process parameters to ensure complete dissolution. The results of process evaluation studies performed at industrial scale at the commercial manufacturing site have been provided, including the process changes made during technology transfer to the commercial site.

The manufacturing process has been satisfactorily validated. All results met the validation acceptance criteria. The in process controls are adequate for this oral solution presentation.

The batch analysis data on 3 consecutive full-scale batches show that this pharmaceutical form can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation

- Control of excipients

With the exception of Mono/Diglycerides of Caprylic/Capric Acid (Capmul MCM) and the two flavours (Buttermint and Butter Toffee) the inactive ingredients are compendial excipients controlled according to the requirements of the current Ph Eur monographs. Sucralose is an excipient not described in the Ph Eur or in any pharmacopoeia of a Member State. It is controlled according to the requirement of the NF. For control of Capmul MCM in house specification based on the USP compendial procedures and official methods from the American Oil Chemist's Society (AOCS) are used. The two flavours (Buttermint and Butter Toffee) comply with legal requirements for food flavourings and are controlled by appropriate in-house specifications.

- Product Specification

The product specifications include tests by validated methods for description, identification (HPLC, UV), assay of the active substance (HPLC), assay of ascorbic acid (HPLC), degradation products (HPLC), examination for tipranavir: 1,3-dioctanoylglycerol solvate (microscopy and visual), microbial limits and efficacy of antimicrobial preservation. Since the product has been shown to have inherent antimicrobial properties, testing for efficacy of antimicrobial preservation will only be performed for stability testing of the first three production batches.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on 13 batches confirm satisfactory uniformity in the product at release.

- Stability of the Product

Stability data have been provided from formal stability studies (one supportive batch, three primary stability batches, four production batches), stress studies (thermal cycling, photostability) and from in-use stability studies.

Results for the supportive stability study were available for up to 24 months storage at long-term condition (25°C/60%RH), 12 months storage at intermediate conditions (30°C/70%RH) and 6 months storage at accelerated (40°C/75%RH) conditions.

Primary batches were stored in the "upright" position and in the "on-the-side" position. Results for the primary stability study were available at the long-term condition up to 36 months storage in the "upright" position and 18 months storage in the "on-the-side position". Results were also available for both positions at the intermediate condition up to 12 months storage, and at the accelerated condition up to 6 months storage.

Production scale batches were studied in the on-side orientation and three of them were stored in both upright and on-side orientations. Results were available up to 24 months at 25°C/60%RH, 12 months at 30°C/70%RH, and 6 months at 40°C/75%RH in both upright and on-side orientations.

Photostability testing was conducted in accordance with the current guideline. Drug product packaged in both clear quartz bottles and in the proposed commercial amber glass bottles as well as two similarly packaged light-protected samples (to serve as dark controls) were concomitantly subjected to light exposure. Results showed that the drug substance is not light sensitive. However, the levels of

ascorbic acid decreased during the study. Therefore, an amber glass bottle has been chosen to protect from light and to minimize the oxidative degradation of ascorbic acid and Vitamin E TPGS.

Thermal cycling stability testing was performed to evaluate the effect of extremes of high and low temperatures that may be encountered during shipping and handling of the drug product. Two different cycles were carried out: freeze-thaw (between –20°C and 40°C/75% RH) and refrigerate-warm (between 4°C and 40°C/75% RH). Cycling conditions showed that that no additional precipitation will occur.

In addition in-use stability studies were also performed. Tipranavir is chemically stable during the in-use period. Assay results did not vary throughout the study and degradation products were detected at levels well below the reporting threshold. In-use antimicrobial preservative effectiveness and microbial limit tests were performed during the study. Microbial limit testing of samples met Ph Eur requirements. The Ph Eur compendial preservative effectiveness tests were supplemented with a simulated in-use test that lasted for the duration of the intended in-use shelf life. Microbiological effectiveness of the preservative system was demonstrated in this study.

Based on available results from stability studies, an expiration period as stated in the SPC, has been approved. In addition The following storage statements "Do not store below 15°C, do not refrigerate or freeze" have been proposed because it has been demonstrated that low temperatures accelerate tipranavir 1,3-DOG crystals formation.

An in-use storage period of 60 days is recommended after first opening of the bottle.

Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacture and control is essentially the same as that reviewed for Aptivus 250 mg soft capsules.

The development of the formulation and manufacturing process for the finished product has been performed with a view to the main variables that could compromise the efficacy and safety of the product solubility and stability of the active substance in the oral solution. The information presented indicates that the product is manufactured and controlled in a consistent way, and should perform consistently in the clinic, from batch to batch.

3. Non-clinical aspects

No module 4 was submitted in this application since no new pre-clinical study had been performed. However, the MAH submitted a non-clinical overview related to the Aptivus oral solution in the setting of Aptivus II/29 application.
In order to support this line extension and the paediatric indication, the MAH provided:

- a discussion on the safety of use of TPV in the children 2 years of age and older, based on non clinical data derived from the MAA of TPV 250 mg capsules,
- a discussion on potential effects on coagulation, derived from non clinical studies performed after MA was granted,
- an environmental risk assessment (ERA), taking into consideration a possible significant increase of environmental exposure to the drug substance.

Review of the nonclinical data supporting the use of TPV oral solution in paediatric patients

At the time of initial MAA, a complete toxicological programme was performed with TPV. It included single dose studies (mice, rats and dogs), repeated dose studies (TPV alone in mice, rats and dogs and TPV + RTV in rats and dogs), genotoxicity and reproductive and developmental toxicity studies (rats and rabbits). Effects of TPV in repeat-dose toxicity studies with TPV were observed primarily in the liver, the gastrointestinal tract, the coagulation system and the testes. Liver was a target organ of TPV in all species tested: rats, mice and dogs. Hepatic effects of TPV common to all species included

increased liver weights and hepatocellular hypertrophy. Testicular effects consisted of decreased weights and bilateral seminiferous tubule degeneration and/or atrophy observed in a 26-week TPV/r study in rats at a dose level of 1200/320 mg/kg/day TPV/r and in the 39-week study in dogs after administration of 320 mg/kg/day TPV alone. Further review of these findings led to the conclusion that the testicular effects were not attributable to TPV. Lymphocytolysis was also observed. An immunotoxicity study has been conducted in mice treated for 28 days to TPV/r the highest dose being 300/80 mg/kg. TPV/r had no effect on the antibody response following immunisation with a T-cell dependent antigen.

When assessing the need for additional toxicity studies in juvenile animals, differences between children and adults in the structure and function of organ systems resulting from growth and development should be considered to determine if the standard battery of toxicology studies is sufficient. Several organ systems are not of concern in children aged 2 years and older due to their maturation at an earlier time point (e.g. pulmonary and renal systems), or the lack of effects on these systems in the standard battery of repeat dose toxicology studies (e.g. skeletal system). Although the nervous system continues to develop until puberty, safety pharmacology studies and repeated dose toxicity studies did not raise any safety concern related to nervous central system in adults, and therefore this organ system is not considered to be potentially affected in the juvenile population.

Safety concerns pertaining to the immune and reproductive systems could be expected in the juvenile population. However, additional data provided during the initial MAA evaluation were reassuring. Finally, since liver is in a mature state in children aged 2 years, no difference is expected in hepatotoxicity in children compared to adults. Therefore, in accordance with the "Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications" (EMEA/CHMP/SWP/169215/2005), the CHMP agreed that there was no need to perform any further study in juvenile animals.

Discussion on potential effects on coagulation, derived from non clinical studies performed after MA was granted

Since the initial MAA, two investigative studies in male rats were performed to evaluate the effects of TPV on the coagulation cascade and to determine if vitamin E-TPGS, an esterified derivative of vitamin E present in TPV oral solution, would modulate the changes induced by TPV. Bleeding events were observed, associated with prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) and a decrease in some vitamin K dependent factors. Coadministration of TPV with vitamin E-TPGS resulted in an exacerbation of the anticoagulant effects of TPV, specifically causing increases in PT, aPTT, and Thrombotest levels and decreases in vitamin K dependent factors. This information was included in the SPC (Variation II/23 – Commission Decision on 7 July 2008) and is included in the SPC for Aptivus oral solution.

Environmental Risk Assessment

The CHMP endorsed the MAH's position who considered that an ERA was not required for this extension application, taking the following into consideration:

- Some adults are expected to shift their treatment from capsules to OS. In this case no increase in the use of TPV applies.
- Children are a potential additional patient group. However, only few children are expected to be treated with TPV OS, since TPV capsules and OS are indicated for patients who are highly treatment experienced.

Thus, no significant increase of environmental exposure to TPV is expected by the use of the OS.

Discussion on the non-clinical aspects

TPV has undergone an extensive nonclinical toxicity testing program in multiple laboratory animal species to support the administration to adults and paediatric patients. There were no clinically relevant effects of TPV, or TPV co-administered with RTV on any of the organ systems considered to be of special concern in relation to juveniles (nervous, reproductive, pulmonary, renal, skeletal, and immune systems). Therefore, the data generated in the comprehensive set of nonclinical toxicology studies supports the administration to paediatric patients.

4. Clinical aspects

Pharmacokinetics – Bioequivalence in adults

In support of this line extension application, the MAH referred to two studies performed to assess the relative BA of TPV oral solution compared to TPV capsules:

- Study 1182.45, submitted within the original MAA for Aptivus
- Study 1182.100, submitted in the framework of FUM 022

Both studies, performed in accordance with GCP as claimed by the MAH, were previously assessed by the CHMP. They are presented and discussed hereafter.

Study 1182.45

This was an open-label, randomised, single-dose, 3-period crossover study with 30 healthy adult volunteers (18 males/12 females), who were given TPV 500 mg SEDDS capsules oral fasted (A); TPV 500 mg Liquid solution oral fasted (B) and TPV 500 Liquid solution oral fed (C) (each together with the commercially available RTV formulations, Norvir capsules or oral solution at a dose of 200 mg). Relative BA of TPV/r 500/200 mg capsules was determined in the fasted state and TPV/r 500/200 mg oral liquid formulations in the fasted and fed (high-fat breakfast) state. A wash-out phase of 7 days was applied. Subjects were randomly assigned to 6 treatment sequences; all 30 subjects completed the study.

Blood samples were collected for 72 hours and urine samples for 24 hours post-dose. Plasma concentrations were quantified by means of the validated bioanalytical method. Beside PK evaluations safety and tolerability were monitored. The statistical model used for the analysis of AUC_{inf} and C_{max} was an ANOVA (analysis of variance) model on the logarithmic scale. This model included effects accounting for the following sources of variation: "sequence", "subject within sequence", "period" and "treatment". A two-sided 90% confidence interval was calculated.

Results

The results of the study are depicted in the following tables; figures indicating bioinequivalence according to the criteria detailed in the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" are highlighted in bold.

Table 1: Results for TPV (fasted oral solution vs fasted capsule)

Test	Parameters	Results
ANOVA	C_{max} $AUC_{0\text{-}inf}$	**sequence effect**
Ratio	C_{max} $AUC_{0\text{-}inf}$	**150%** **137%**
Standard CI 90%	C_{max} $AUC_{0\text{-}inf}$	**1.40 - 1.60** **1.30 - 1.43**

Table 2: Results (fed oral solution vs fasted capsules)

Test	Parameters	Results
ANOVA	C_{max} $AUC_{0\text{-}inf}$	**period and sequence effect**
Ratio	C_{max} $AUC_{0\text{-}inf}$	107% **130%**
Standard CI 90%	C_{max} $AUC_{0\text{-}inf}$	1.00 - 1.14 **1.23 - 1.36**

Table 3: Results (fed oral solution vs fasted oral solution)

Test	Parameters	Results
ANOVA	C_{max} $AUC_{0\text{-inf}}$	**period and sequence effect**
Ratio	C_{max} $AUC_{0\text{-inf}}$	**71%** 95%
Standard CI 90%	Cmax $AUC_{0\text{-inf}}$	**0.67 - 0.76** 0.90 - 1.00

In the fasted state, BE could not be shown between the capsule and the OS: the OS was significantly supra-bioavailable (AUC: +37%; C_{max}: +50%).

The OS given in fed state was supra-bioavailable (by 30% for AUC and 7% for C_{max}) in relation to the capsule given in fasted state.

From the data presented the CHMP considered that the BE of capsule and oral solution was not demonstrated. Therefore, no appropriate dosing recommendation could be given. Based on the PK data derived from the study performed it could only be concluded that a decrease in the dosing regimen for the OS will likely be required to obtain TPV plasma concentrations equivalent to those obtained with the capsules. The relative BA between OS with food and capsules with food was not performed although the current SPC mentions that TPV capsules should be taken with food.

Study 1182.100

Design

This was an open label, one-sequence, non-randomised, cross-over study evaluating the relative bioavailability of the TPV/r OS to the capsule formulation at steady-state with both treatments under fasted and fed conditions in 35 healthy male (n=17) and female adult volunteers, 32 of which completed the study and were included in statistical evaluations. Volunteers who had successfully participated in previous studies tolerating TPV were selected, where possible. A subject enrolled in the study was supposed to receive 21 doses (q12h) TPV/r capsules followed by 8 doses (q12h) oral solution (see Figure 1).

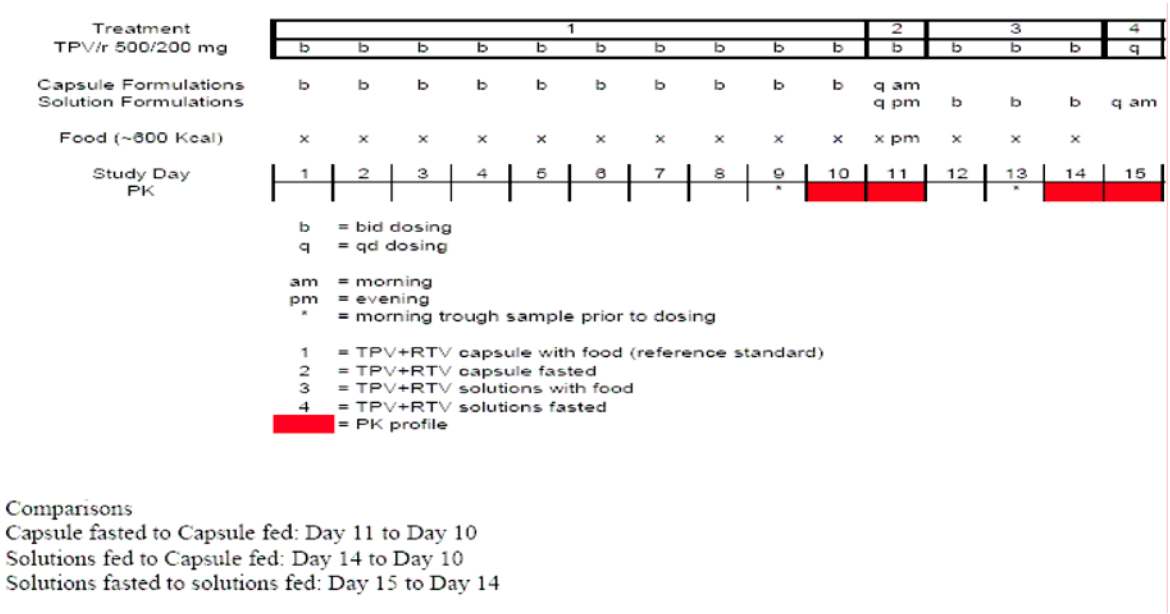

Figure 1: Design of study BI 1182.100

Discussion on the study design

The CHMP highlighted that the cross-over of the study was done in a non-randomised way therefore violating one of the main prerequisites of a state-of-the-art BE testing and making the period effect non-assessable. The results of the non-randomised trial clearly indicate differences between formulations but it is not possible to conclude that the observed differences are irrelevant, because it could be, that a "negative" period effect has actually already diminished the true difference between formulations to the observed degree (i.e. the true difference can be even larger). Accordingly, the study results are considered neither reliable nor interpretable. The absence of wash-out period was considered inappropriate since the effect of interfering factors on the measured plasma concentration could not be excluded.

According to the MAH, this study design was preferred mainly because the oral solution is significantly less palatable than the capsule formulation. This justification was not endorsed by the CHMP since the oral solution has been primarily developed for paediatric patients and, in general, patients who will receive this formulation are likely to be more sensitive to palatability than healthy volunteers. The CHMP also noted that recruiting mainly volunteers who tolerated TPV in previous studies preclude a reliable safety and tolerability evaluation by introducing a bias.

Results

Pre-dose and 11 post-dose blood samples were obtained within the 12 h dosing interval. Pair wise comparisons of TPV (and RTV) after each mode of administration were performed with 90% confidence intervals derived from the logarithmic scale. The primary comparison was AUC_{0-12h} of the TPV/r capsules and the oral solution both administered in the fed state. Results are presented in the following tables; figures indicating bioinequivalence are highlighted in bold. No comparison of PK in the fasted state was performed in the study.

Table 4: Summary of geometric mean ratios and 90%-confidence intervals for TPV/r 500/200 mg oral solution administered with and without food

PK parameter	Geometric mean ratio (%) TPV/r solution fasted versus fed	90 % confidence interval
TPV		
Cp12h	95.60	90 – 102 %
C_{max}	120.74	**116 – 126 %**
AUC_{0-12h}	102.91	100 – 106 %
RTV		
Cp12h	89.84	81 – 100 %
C_{max}	182.36	**165 – 201 %**
AUC_{0-12h}	135.43	**125 – 147 %**

Table 5: Summary of geometric mean ratios and 90%-confidence intervals for TPV/r 500/200 mg capsules administered with and without food

PK parameter	Geometric mean ratio (%) TPV/r capsules fasted versus fed	90 % confidence interval
TPV		
Cp12h	101.50	84 – 123 %
C_{max}	101.64	91 – 114 %
AUC_{0-12h}	99.17	88 – 112 %
RTV		
Cp12h	83.11	67 – 103 %
C_{max}	126.55	**95 – 168 %**
AUC_{0-12h}	103.88	**79 – 134 %**

Table 6: Summary of geometric mean ratios and 90%-confidence intervals for TPV/r 500/200 mg capsules and solutions administered with food

PK parameter	Geometric mean ratio (%) TPV/r fed conditions oral solution versus capsule	90 % confidence interval
TPV		
Cp12h	128.26	**110 – 150 %**
C_{max}	114.33	**103 – 126 %**
AUC_{0-12h}	122.64	**111 - 135 %**
RTV		
Cp12h	71.77	**60 – 86 %**
C_{max}	86.77	**70 – 107 %**
AUC_{0-12h}	96.11	**79 – 118 %**

Study 1182.100 showed a supra-bioavailability of TPV OS compared to the capsule formulation in the fed state.

This supra-bioavailability was however significantly less noticeable than observed in Study 1182.45 in the fasted state (AUC: +23% *versus* +37% and C_{max}: +14% *versus* +50%). When taking into consideration the upper limit of the confidence interval for AUC (i.e. +35%) and the fact that appropriate food intake may be limited in some patients, these findings may have a clinical impact. For the OS administered with food, TPV C_{max} was decreased by approximately 20% compared to the fasted state, whereas AUC was not altered. No significant food effect was observed in this study for the capsule formulation.

With regard to RTV, an important food effect was observed with the OS, the BA being significantly increased in the fasted state (ratio fasted/fed: C_{max}: 182 %; AUC: 135 %). A similar trend was observed for the capsule formulation though being less significant. These findings were considered conflicting by the CHMP given that concomitant food intake is recommended for the RTV OS (see Norvir SPC). Besides, despite the decrease in RTV exposure, TPV exposure appeared enhanced. These results may question the appropriateness of the TPV/r ratio for the oral solution although the TPV/r ratio proposed for paediatrics is similar as the one previously approved for adults.

Discussion on PK in adults

Both Study 1182.45 and Study 1182.100 failed to demonstrate BE between the OS and the capsule formulation. Rather, they showed that the OS is significantly supra-bioavailable when compared to the capsule formulation. While this effect was less pronounced in the latter study that compared BA of both formulations in the fed state, the lack of BE demonstration renders impossible the conclusion on a valid dosing based on extrapolation of capsule data for the OS in the adult population. Therefore based on the data presented the oral solution cannot be considered for the treatment of the adult population.

Pharmacokinetics and clinical efficacy - Paediatric Trial 1182.14

The pharmacokinetics of TPV OS and capsules were examined in HIV-1 infected patients in Trial 1182.14, in a formal PK substudy among 52 patients, and subsequently in all patients, using trough sampling (for a full discussion, please see EMEA/H/C/631/II/29). In this trial, all children were to begin dosing using OS. After the first 28 days of dosing, older, larger children were allowed to switch from OS to capsules, provided that their calculated dose reached TPV/r 500 mg/200 mg b.i.d.

Children were randomised between two dose groups based on body surface area (BSA). A lower TPV/r dose of 290mg/115mg per m^2 was compared to the higher dose of 375mg/150mg per m^2 b.i.d. Children continued on these doses for 48 weeks. Whereas predefined pharmacokinetic criteria would have supported the selection of the lower dose, a full trial analysis, including also efficacy and safety, was performed based on 48 week data, which resulted in the high dose being chosen definitively as the desired dose.

Tables 7 summarises key PK findings from the 48 week analysis. As anticipated, the TPV concentrations were higher in the high dose group than the low dose group. Furthermore, it demonstrated the broad range of concentrations observed in patients in the trial. The large coefficients of variance (expressed as percent, or CV%) for steady-state trough values, from 66.8% to 124.5%, underline this.

Table 7: Summary of TPV steady-state PK for paediatric patients receiving TPV/r 290/115 mg/m^2 or 375/150 mg/m^2 – Cmin,ss1 in full trial population, receiving either OS or CAPs

Age (yrs)	Summary Statistic	TPV/r dose (mg/m^2)		Ratio[2]
		290/115	375/150	
2 to <6	N samples	99	44	1.4
	Geometric Mean Cmin,ss (μM)	32.69	46.91	
	Geometric CV%	99.2	66.8	
6 to <12	N samples	120	84	1.9
	Geometric Mean Cmin,ss (μM)	33.08	61.32	
	Geometric CV%	91.9	86.1	
12 to 18	N samples	106	82	1.1
	Geometric Mean Cmin,ss (μM)	49.79	55.06	
	Geometric CV%	115.0	124.5	

CV%: coefficient of variance, expressed as percent

1. concentrations obtained 10-14 hours post-dosing
2. Ratio of geometric mean for High dose / Low dose

These figures show the high variability of TPV PK (CV values close to 100%). This may not only be an inherent characteristic of TPV as such, but could also be an indicator for adherence problems with the oral OS (e.g. due to vomiting). Interestingly, the lower ratio of the geometric mean for high/low dose in the 12-18 year olds as compared to the other age groups may be explained by the maximum dose of 500/200 mg TPV/rtv, which may have been achieved also in a considerable proportion of patients in the low-dose group.

Result at 48 weeks Trial 1182.14

Overall, 45.6% (26/57) patients achieved VL <400 copies/ml in the TPV/r high dose compared to 39.7 % (23/58) in the TPV/r low dose, but the difference was not statistically significant (p=0.57). A total of 34.5% (20/58) patients in the TPV/r low dose group vs. 35.1% (20/57) patients in the TPV/r high dose group achieved <50 copies/ml. Median VL decrease was -0.80 $\log_{10}$ copies/ml in the TPV/r low dose group compared to -1.24 $\log_{10}$ copies/ml in the TPV/r high dose group. The difference between the two doses at Week 48 was not statistically significant. The overall proportion of patients achieving VL decrease ≥1 $\log_{10}$ copies/ml was 43.1% (25/58) in the TPV/r low dose and 45.6% (26/57) in the TPV/r high dose at Week 48 (p=0.85). Both dose groups showed overall increase in CD4 cell count and CD4% through Week 48.

Table 8: Summary of the Week 48 efficacy results

Age group	2 to <6		6 to <12		12 to 18	
Dose	TPV/r low	TPV/r high	TPV/r low	TPV/r high	TPV/r low	TPV/r high
Median VL change $\log_{10}$ copies/mL	-2.74	-2.38	-0.57	-1.24	-0.26	-0.62
VL < 400 copies/mL	76.9%	66.7%	31.6%	42.1%	26.9%	38.5%
VL < 50 copies/mL	53.8%	50.0%	31.6%	42.1%	26.9%	23.1%
VL decrease ≥1 $\log_{10}$ copies/mL	84.6%	66.7%	36.6%	42.1%	26.9%	38.5%
Median CD4 increase	504	140	143	141	25	31
Median CD4% increase	10	6	5	3	2	0

As shown in Table 11 above, a higher proportion of patients achieved VL<400 copies/ml in the 2 to <6 age group than in the 6 to <12 age group and the 12 to 18 age group. Likewise, the proportion of patients with virologic response was higher in younger children (e.g. 50% of patients in the 2- <6 year group achieved VL <50 copies/ml vs. 25% in the 12-18 year group). Although there was an overall trend towards better virological response with the TPV/r high dose, no statistically significant difference was observed. This trend for higher response with the high dose was mainly due to the better results observed in the 6 to <12 years old and 12 to 18 years old age cohorts. In the 2 to <6 year group there was on the contrary a trend for higher virological response with the TPV/r low dose group.

A logistic regression was performed modelling the effects of treatment group, genotypic inhibitory quotient (GIQ), baseline viral load, age group, TPV adherence, and genotypic sensitivity score (GSS) on the outcome at Week 48 for the three virologic endpoints of HIV RNA <400 copies/ml, HIV RNA <50 copies/ml, and ≥1 $\log_{10}$ reduction of HIV RNA from baseline.

Higher baseline resistance tended to result in a lower proportion of virologic responders. Increasing TPV mutation scores were associated with decreased rates of virologic response, particularly for the low dose patients. In those patients with more baseline resistance mutations, the high dose groups had higher viral response rates, especially in the group with ≥5 TPV mutations.

Table 9: Proportions of patients with virologic response (<400 copies/ml) at Week 48 by baseline TPV mutation score (FAS 48)

Baseline TPV Mutation Score	Low Dose n (%) N	High Dose n (%) N
0	6 (85.7) 7	4 (33.3) 12
1 to 4	16 (44.4) 36	17 (51.5) 33
5 or more	1 (6.7) 15	5 (41.7) 12
Total	23 (39.7) 58	26 (45.6) 57

The GIQ is a reflection of TPV concentration and baseline resistance to TPV. It was determined for each patient by dividing the geometric mean of TPV C_{trough} obtained at steady state by the number of TPV mutations present at baseline. Patients with the largest number of TPV mutations (i.e. patients with more advanced infections and more extensive prior treatment) had the lowest GIQ values.

However, this baseline resistance was countered in the high dose group by the achievement of higher concentrations of TPV. Overall, the median GIQ values were larger among TPV/r high dose-treated patients (12.33 for low dose vs. 19.04 for high dose), a trend that was observed within each age group as well. Moreover, among the age groups, the 2 to <6 year-olds exhibited the largest median GIQ score, with the 6 to <12 year-olds given high dose TPV/r having a lower score, followed by 12 to 18 year-olds having the lowest score, reflecting that the younger children had fewer baseline mutations, which translated into higher GIQ and thus higher virologic response rates.

Table 10: Virologic response at Week 48 based on the GIQ quartiles

GIQ quartiles	<400 copies/mL n (%) N	<50 copies/mL n (%) N	≥1 $\log_{10}$ copies/mL n (%) N
Q1 (0.56-7.19)	2 (8.0) 25	1 (4.0) 25	2 (8.0) 25
Q2 (7.23-13.50)	13 (52.0) 25	11 (44.0) 25	14 (56.0) 25
Q3 (13.68-38.61)	15 (57.7) 26	13 (50.0) 26	16 (61.5) 26
Q4 (39.29-215.38)	17 (68.0) 25	14 (56.0) 25	17 (68.0) 25

Multivariate analyses revealed that GIQ level and adherence to treatment were each statistically significant predictors of viral load response. When these parameters were included in the model, age was no longer an important factor. Overall, higher GIQ scores led to higher odds ratios for response compared to the lowest GIQ quartile. This suggests that treatment response can be improved by using the higher dose of TPV/r, resulting in an increase in TPV concentration and a higher GIQ.

Four (4) patients, all in the TPV/r low dose group, developed an AIDS defined illness. Kaplan-Meier probability of reaching an AIDS defining illness up to Week 48 was 7.8% in the TPV/r low dose group vs. 0.0% in the TPV/r high dose group (p = 0.04).

Discussion on the 48-week results
The MAH concluded that TPV/r high dose, TPV 375 mg/m^2 + RTV 150mg/m^2, is the appropriate dose for paediatric patients aged 2 to 18 years as it provided a higher and more durable response with an acceptable safety profile. Therefore, although the interim analysis results at 24-week led to selection of the TPV/r low dose, all patients were switched to the TPV/r high dose following analysis of the 48-week results.

Theses changes highlight the difficulty of identifying the appropriate dosing based on a rational argument as overall the results were not consistent across the different age groups: the low dose gave better response rate in the 2-6 and in the 12-18 age groups whereas the high dose gave better response rate in the 6-12 age group.

However, when analysing the efficacy results for both dose groups by 48 weeks for all age groups, the percentage of patients with VL <50 copies/ml, results were similar for the low dose and the high dose (34.5% and 35.1%, respectively). This inconclusiveness of findings, not giving a clear picture on the effective dose within a good safety margin, highlights the paucity of the available data.

Specifically for the 12-18 year-old patients, only a small virologic impact was observed, i.e. -0.26 in TPV/r low dose group to -0.62 $\log_{10}$ copies/ml in the TPV/r high dose group (-0.2 in the oral solution group and -0.4 in the capsule group). Nevertheless, comparison with other clinical trials of ritonavir boosted PIs show similar results. For all of them, efficacy results markedly decreased for adolescents when compared to children.

GIQ and adherence were shown to be significant predictors of Week 48 response rates while the age group was not a significant predictor. For this reason, the MAH believes that the higher dose of TPV/r is appropriate, especially for children who fulfil the current indication for TPV/r, and are infected with HIV that has failed prior therapy.

In principle, the CHMP considered the use of the dose that provides the higher GIQ in this target population with viral strains harbouring multi-resistance reasonable. However, clinical data to substantiate this dose in children remain limited.

Taking into account the effect on viral load, and the differences in the safety profiles due to the composition of the oral solution that may further compromise the product's safety (cf. Discussion on excipients), TPV/r may still have a place, even if very limited, in the treatment of HIV infected children harbouring a multi resistant virus. In view of the limitations of the PK and clinical data in children with the recommended dose TPV/r as oral solution can be only considered for the treatment of children from 2 to 12 years of age as a last line therapy when no other therapeutic options are available. Patients reaching 12 years could then be switched to the capsules (see assessment of II/29).

Efficacy results at Week 100
As discussed above, based on the 48-week data, the MAH selected the TPV/r high dose for the continuation of the study, i.e. patients who were on low dose from the beginning of the trial and those who were on high dose and switched to low dose after the first interim analysis received the TPV/r high dose after Week 48.

Results
The 100-week efficacy analyses were mainly focussed on the comparison of the two formulations (oral solution and soft capsules) but not on the different dose regimens investigated in the first 48 weeks of the study. Changes from baseline in viral load, CD4 and CD4% and virological response rates are summarised in Tables 7 and 8 respectively.

Table 11: Median change from baseline for virologic and immunologic parameters for TPV/r treated patients, by age group and formulation

	TPV OS			TPV SEDDS
	2-<6 yrs N (%)	6-<12 yrs N (%)	12-18 yrs N (%)	12-18 yrs N (%)
Total treated	25 (100.0)	37 (100.0)	24 (100.0)	29 (100.0)
Median VL log_{10} copies/mL change from baseline - (LOCF)				
Baseline [1]	5.0	4.6	5.1	4.6
Week 24	-2.5	-1.7 [2]	-0.4	-1.2
Week 48	-2.7	-1.0 [2]	-0.4	-0.8
Week 100	-2.7	-1.2 [2]	-0.2	-0.4
Median CD4+ cell count (cells/mm^3) change from baseline - (LOCF)				
Baseline [1]	795	398	208	330
Week 24	293	133	24	56
Week 48	323	143	21	39
Week 100	294	121	12	45
Median CD4% change from baseline - (LOCF)				
Baseline [1]	26	19	12	19
Week 24	7	4	1	2
Week 48	7	5	1	3
Week 100	6	4	1	0

1 Represents baseline values and not a change from baseline
2 ANOVA p≤0.05 comparing OS treated 2 - <6 and 6 - <12 year old patients

Table 12: Proportion of TPV/r treated patients with viral response, by age group and formulation

	TPV OS			TPV SEDDS
	2-<6 yrs N (%)	6-<12 yrs N (%)	12-18 yrs N (%)	12-18 yrs N (%)
Total treated	25 (100.0)	37 (100.0)	24 (100.0)	29 (100.0)
Number of patients with at least 1 log_{10} VL reduction - (NCF)[1]				
Week 24	20 (80.0)	18 (48.6) [2]	9 (37.5)	13 (44.8)
Week 48	19 (76.0)	14 (37.8) [2]	8 (33.3)	9 (31.0)
Week 100	14 (56.0)	13 (35.1)	6 (25.0)	7 (24.1)
Number of patients <400 copies/mL - (NCF) [1]				
Week 24	16 (64.0)	15 (40.5)	8 (33.3)	10 (34.5)
Week 48	18 (72.0)	13 (35.1) [1]	8 (33.3)	9 (31.0)
Week 100	14 (56.0)	11 (29.7) [2]	6 (25.0)	7 (24.1)
Number of patients <50 copies/mL - (NCF) [1]				
Week 24	10 (40.0)	12 (32.4)	6 (25.0)	8 (27.6)
Week 48	13 (52.0)	31 (35.1)	6 (25.0)	8 (27.6)
Week 100	12 (48.0)	11 (29.7)	5 (20.8)	6 (20.7)

1 NCF = Non-Completers considered Failures
2 Fisher's exact p≤ 0.05 comparing OS treated 2-<6 and 6-<12 year old patients
3 Fisher's exact p=0.06 comparing OS treated 2-<6 and 6-<12 year old patients

Discussion on the 100-week results

The week 100 results shoed overall a low response, with a marked difference between the 2 age groups: a Log 10 VL reduction was achieved in 56% for 2-6 years group and 35.1% in the 6-12 year group. These results were also reflected in the secondary endpoints i.e VL> 50/400 copies/ml.

According to the MAH, these results suggest a comparable efficacy between the two TPV formulation treatment groups based on the NCF analysis of the number of patients with VL reduction <400, <50 copies/ml and at least 1 $\log_{10}$ sustained VL reduction from baseline virologic endpoints. The results also showed an advantage among capsule treated patients over oral solution treated patients LOCF median changes from baseline in virologic and CD4-cell endpoints.

Due to the design of study, in particular in view of the 'non-randomised' switch of formulations in the 12-18 year group, a valid comparison is difficult. Therefore, the CHMP could not conclude on the therapeutic equivalence of the two formulations based on the above results. Overall, the response rate in this study was significantly low. In both formulation groups, only approximately 20% of the 12-18 year-old patients had VL <50 copies/ml at week 100 (NCF), which is considered worrying. The 100-week efficacy data confirmed a lower virologic response in the 12-18 year group compared to younger groups.

Since the switch from oral solution to soft-gelatin capsule was conducted in a non-randomised manner, patients staying on oral solution can be considered as pre-selected in terms of tolerability of the liquid formulation. Nevertheless, globally the capsule compares favourable to the oral solution.

Overall discussion on efficacy

Both Study 1182.45 and Study 1182.100 failed to demonstrate BE between the OS and the capsule formulation. Rather, they showed that the OS is significantly supra-bioavailable when compared to the capsule formulation. While this effect was less pronounced in the latter study that compared BA of both formulations in the fed state, the lack of BE demonstration renders the conclusion on a valid dosing based on extrapolation of capsule data for the OS in the adult population impossible.

Also, the high impact of food on the relative BA of the OS highlights the necessity to carefully control the intake, especially in patients with limited food intake. As the MAH proposed an indication in patients who are experiencing difficulties in swallowing, this is especially problematic, as intake of OS in fasted conditions could particularly lead to over-exposure and therefore to a worsening of the safety profile. In view of the better tolerability of the OS, the recommendation to take TPV with food should remain in the SPC; here, a claim of BE between fed and fasted state cannot be accepted based on the presented data. Therefore, the indication of the OS was restricted to exclude the adult population.

In addition, the difference between relative BA of the two formulations raised concerns for patients switching between one and the other, especially children having reached the adult dosing of TPV/r 500/200mg b.i.d., who could potentially experience a sudden decrease in TPV exposure when changing to the capsule formulation. Data provided by the MAH for the 12-18 year old children, having received first the OS and then the capsules, are reassuring since there is no apparent deterioration of the efficacy results in these patients switching from the oral solution to the capsule. Therefore, it can be accepted that no specific dose-adjustment is proposed in case of switch from the oral solution to the capsules in paediatric patients (i.e. getting 12 years while already on TPV therapy).

Taking into account the effect on viral load observed in Trial 1182.14, TPV/r may have a place, even if very limited, in the treatment of HIV infected children harbouring multi resistant virus. In view of the limitations of the PK and clinical data in children with the recommended dose TPV/r as oral solution can be only considered for the treatment of children when no other therapeutic options are available. The need for deep salvage therapy is mainly expected to be observed in adolescents and not in younger children (apart for the situation of transmission of multi-resistant strain from the mother),. Overall, the use of TPV/r is expected to be marginal in children below 12 years of age. Indeed, the younger the children are, the less likely is the presence of HIV harbouring multiple PI resistance mutations. However, TPV/r could potentially address a medical need in situations of last-line therapy for younger ages. As for the adult population and the capsule formulation, this medicinal product can be only considered as a last line therapy and only in children from 2 to 12 years of age whose viral

strain does not harbour mutations known to impact TPV's efficacy. Patients reaching 12 years should switch to the capsule formulation.

Clinical safety

Apart from the bioequivalence study, no specific clinical safety study has been provided. However, reference has been made to the paediatric study 1182.14 (please refer to the assessment report of procedure II/29).

In Study 1182.45, 25 of the 30 subjects reported a total 60 adverse events (AEs). Of these, 46 were considered treatment-related. All AEs were mild or moderate in intensity. Gastrointestinal events, such as abdominal pain, diarrhoea, nausea and dyspepsia were the most frequent events assessed to be treatment-related. Headaches and dizziness were also reported. There were no significant safety issues relating to vital signs, ECG findings and physical examination or laboratory safety tests.

Discussion on the excipients

The concentrations of excipients in the oral solution as listed in the TPV and RTV SPC were examined and several exceeded acceptable daily intake limits. The latter include vitamin E as administered in Vitamin E TPGS and PEG 400. The major excipients in the formulation are discussed below.

Propylene glycol (PG)

The EMEA guideline on excipients (Volume 3B Guideline. Medicinal product for human use. Safety environment and information. 2003) gives guidance regarding the use of propylene glycol. The thresholds for this substance are 400mg/kg for adults and 200mg/kg for children. The threshold level is 200 mg/kg/day for children. The level of PG found in TPV oral solution formulation with RTV oral solution co-administration is judged to be safe at less than half the threshold level in children greater than 2 years of age. Toxic effects of PG are similar to those of ethanol intoxication, e.g. stupor, ataxia. At high PG exposure levels, other effects may be noted and include seizures, tachycardia, hyperosmolality, lactic acidosis, and renal toxicity.

Overall, as regards to PG it is showed that the maximum daily uptake when using TPV oral solution remains well below the limits defined for safety reasons.

Capmul MCM

Capmul MCM, is a proprietary mixture of glyceryl caprate (C_{10}) and glyceryl caprylate (C_8), which are medium chain monoglycerides. Mono- and triglycerides are absorbed into the intestinal cells where they are largely converted back to triglycerides. The Joint FAO/WHO Expert Committee on Food Additives has concluded that there is no evidence that the presence of mono- or diglycerides of food fats has any deleterious effect on cells or tissues. Mono- and diglycerides are consumed daily in diets containing fat and no harmful effects have been specifically associated with mono- or diglycerides. Furthermore, the mono- and diglycerides most likely to produce unwanted effects are those containing long-chain saturated fatty acids (*e.g.*, stearic acid). Thus, as glyceryl caprate and glyceryl caprylate are natural constituents of the human diet and human triglyceride metabolism, their presence as a mixture in Capmul MCM is not expected to cause safety concern.

Overall Capmul is considered a non-critical excipient regarding its safety in humans; therefore, no upper intake limits have been established.

Vitamin E polyethylene glycol succinate (Vitamin E TPGS)

Vitamin E TPGS is a water-soluble form of natural-source vitamin E prepared by esterifying d-alpha-tocopheryl acid succinate with polyethylene glycol 1000.

The safety of TPGS as a food supplement is described by the European Food safety Authority (EFSA). The NOAEL was defined as 1000mg/kg/day based on the data obtained in rats and mice. In rats extremely high dosages (2000 mg/kg/day) lead to longer prothrombin and thromboplastin times. In rats an antagonistic effect between vitamin E and vitamin K was observed. In rats which received 2000 mg/kg/day and were deprived from Vitamin K hemorrhages were observed.

Safety of vitamin E intake has also been reviewed by the NIH and Hathcock *et al*. In humans no consistent side effects are associated with chronic vitamin E usage even at high dosages (<3600IU/day) as demonstrated in clinical trials. In one of these trials no significant side effects were found in a double-blind crossover study involving 52 patients, who received daily amounts of 1600 IU RRR-alpha-tocopheryl succinate over 6 months. No difference in prothrombin time was observed. High levels of Vitamin E can exacerbate the blood coagulation effect of Vitamin K deficiency. There are several reports of undesirable effects of vitamin E such as fatigue and muscle weakness in case reports which could not be confirmed in controlled clinical trials.
The NIH has defined the tolerable intake level (UL) of vitamin E in adults at 1500 IU (1000 mg alpha tocepherol) which is the highest dose unlikely to result in bleeding problems. These levels are based on the lowest-observed-adverse-effect-level (LOAEL) in animals (500 mg /kg) corrected with a safety factor.

Ten (10) ml TPV solution (maximum dose) contains a higher level of Vitamin E (d-alpha-tocopherol) than the recommended daily intake and thus can be considered an overdose. The exposure in adults is lower than the acceptable limit stated by the NIH which is 14 mg/kg/day, while the exposure in children exceeds the limit set by the NIH. Therefore, an overdose can be expected with the water-soluble form of vitamin E contained in TPV OS.

Signs of acute vitamin E overdose can include gastrointestinal disturbances such as nausea and diarrhoea or headache. Chronic overdose may result in muscle weakness and fatigue. Although the AEs reported in study 1182.45 were not considered to be specific, the CHMP pointed out that a relationship between these events and the vitamin E content of the oral solution could not be excluded.
Data from Trials 1182.14 and RESIST 1 and 2 (1182.12 and 1182.48 indicate that the PT, aPTT and coagulation factor levels and activity (Factors II, V and VII) are not affected by TPV/r administration in humans. Furthermore, there was no effect on these coagulation parameters with the use of vitamin E-containing TPV/r oral solution in children. An analysis of clinical bleeding events was performed in the 100 week analysis of the 1182.14 clinical trial report, to determine whether the vitamin E-containing OS resulted in increased risk of bleeding, compared the capsule formulation. All frequencies of occurrence of clinical bleeding AEs (Bleeding medically selected terms [MSTs]) were compared among the 12-18 year old children who took OS and the 12-18 year olds who took capsules cumulatively through the week 48 analysis and the week 100 analysis. In neither analysis was there evidence of increased risk of these events in the OS recipients (48 weeks: 1/25 (4.0%) vs 4/28 (14.3%) for OS and capsule recipients, respectively; 100 weeks: 4/25 (16.7%) vs 4/29 (13.8%), respectively). Furthermore, among children less than 12 years, all of whom received OS, the proportions with MST bleeding events was lower (4/62 (6.5%) and 5/52 (9.6%) for the weeks 48 and 100 analyses). Most of these events were relatively minor, such as epistaxis, haematomas, and gingival bleeding.

Overall, most of the study data presented by the MAH were derived from adult patients. The doses applied and formulations used were very variable. From the data presented no clear conclusion can be drawn on whether supplementation with high doses of vitamin E is linked to any increased risk. The submitted information on vitamin E supplementation focused on fat-soluble forms and the main body of evidence on the safety of the water-soluble vitamin E polyethylene glycol succinate, as contained in TPV OS, was gathered in substitution studies. There is evidence that absorption of the water-soluble form is impaired in healthy adults, i.e. those with preserved lipid absorption and normal vitamin E homeostasis. In these subjects, Vitamin E TPGS only slightly elevated the plasma alpha-tocopherol levels. However, the applied doses were much lower than those achieved with TPV OS.

Overall, the provided data show that the maximum daily intake of Vitamin E TPGS in children taking Aptivus OS is much higher than the recommended upper limits. Current available data cannot rule out that this constitutes a risk to the patients.

Polyethylene Glycol 400 (PEG 400)
PEG 400 is considered of low toxicity when administered orally. The exposure to PEG 400 in TPV OS is estimated at ~ 20 fold the WHO Acceptable Daily Intake (ADI).

The anticipated effect of PEG-400 is loose stools/diarrhoea. According to the MAH, this effect did not occur at a higher frequency in volunteers/patients taking TPV OS as compared to those taking capsules. However, study 1182.45 was a single-dose study and the groups of 12-18 year old paediatric patients in study 1182.14 were not randomised to the respective treatment, i.e. selection bias cannot be excluded. Consequently the CHMP was of the opinion that the comparative safety data cannot be regarded as meaningful. Although, no increase in diarrhoea was observed by the MAH when comparing oral solution and capsules in the clinical trials it is anticipated that PEG 400 at this dose level may contribute to an increased incidence of soft stools and/or diarrhoea.

In addition, the PEG-1000 content of Vitamine E TPGS raises additional concern. According to the statement of the EFSA the Scientific Committee on Food and the Joint FAO/WHO Expert Committee on Food Additives established limits for PEG 300-4000 of 5 mg/kg bw/day (body weight per day) and PEG 200-10000 of 10 mg/kg bw/day in infants and children, respectively. Summing up the PEG-400 and the PEG-1000 content in TPV OS would result in PEG levels of 30 to 60-fold the UL recommended by EFSA.

Overall, the provided data show that the maximum daily intake of PEG in children taking Aptivus OS is much higher than the recommended upper limits. Currently available data cannot rule out that this constitutes a risk to the patients.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAH submitted an updated RMP (version 4.2) which was assessed in the framework of the parallel extension of indication variation EMEA/H/C/631/II/29.

6. Risk/benefit assessment, overall conclusions, and recommendation

Benefit

In general, liquid formulations are advantageous in patients unable to swallow solid formulations - adults as well as children - and in those requiring dosage adjustments e.g. children and patients with renal or hepatic impairment. As TPV is contraindicated in patients with moderate to severe hepatic impairment and as no dose adjustment is necessary for patients with renal impairment, the latter benefits are not applicable. TPV is currently authorised for heavily pretreated patients, likely to suffer from advanced immunodeficiency. Some opportunistic infections and other diseases related to severe immunodeficiency, e.g. different forms of oesophagitis, may result in difficulties swallowing the capsules, which may lead to an interruption of the therapy. To circumvent this, development of a liquid TPV formulation is critical. Moreover, the enlargement of the antiviral armamentarium for the treatment of HIV infected children is crucial. This can only be achieved by developing either solid dosage forms of lower strengths or liquid dosage forms to allow for dose adjustment according to weight, size or age.

Risk

As discussed above, bioequivalence between TPV capsules and the oral solution has not been demonstrated. The BE study comparing the two formulations in the fed state (as recommended in the SPC) presented major design issues precluding a reliable assessment of the results. When disregarding these major limitations, suprabioavailability was found with 90% confidence intervals for C_{max} of 103-126% and for AUC_{0-12h} of 111-135%. This overexposure may lead to more severe adverse events

in view of the known safety profile of TPV capsules. This applies especially to the oral solution, where poor palatability of the oral solution and the composition (critical contents of some of the excipients: PEG and Vitamin E TPGS) raise concerns as regards the tolerability and may further compromise the product's safety, in particular with respect to gastro-intestinal and bleeding events.

Balance

Adults unable to swallow TPV capsules:
The supra-bioavailability observed with the OS, when both products were administered under fed conditions (as recommended in the respective SPCs) may lead to more severe adverse events. This is considered not acceptable in view of the worrying safety profile of TPV (e.g. hepatotoxicity and intra-cranial haemorrhages).

Paediatric patients:
Due to the major deficiencies of the study design no conclusion can be drawn from the study as regards the bioequivalence between both formulations. In view on the effect on the viral load of TPV OS the data submitted within this application can be only regarded as favourable in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple proteases inhibitors. The oral solution should be used only in patients without any other therapeutics options. Patients reaching 12 years should then be switched to the capsules (see assessment of EMEA/H/C/631/II/29).

Overall Conclusion

The MAH has developed an oral solution to be used in children as well as in adults unable to swallow the capsules. Even though this oral solution is of interest, it remains that the PK development performed by the MAH suffers from several deficiencies; thus it is currently not possible to establish the condition for a proper inter-changeability between the capsule and the oral solution. Therefore this oral solution cannot be proposed for adult patients who cannot swallow the capsule.

Given the severe safety profile and the complex interaction profile of TPV/r, this boosted PI was only approved for the use in heavily PI-experienced adult patients. Further to the risks identified for the capsules, the oral solution bears some additional risks as stressed above, which led the CHMP to the conclusion that it should be recommended for approval in a limited indication. As for the adult population, this medicinal product can be only considered as a last line therapy and only in children whose viral strain does not harbour mutations impacting TPV's efficacy. A deep salvage therapy situation is mainly expected to be observed in adolescents and not in younger children (apart from the situation of transmission of multi-resistant strain from the mother). The use of TPV/r is expected to be marginal in children and anecdotal in the particular subgroup of children below 12 years. Indeed, the younger the children are the less likely is the presence of HIV harbouring multiple PI resistance mutations. Nevertheless, a medical need for TPV/r in situations of deep salvage therapy for younger ages cannot be excluded. Therefore, the benefit/risk of TPV/r oral solution can be regarded as favourable only in paediatric patients from 2 years to 12 years of age as a last line therapy option and when the approved capsule formulation is not suitable to achieve the currently recommended dose.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Aptivus 100 mg/ml oral solution in the treatment of HIV-1 infection was favourable and therefore recommended the granting of the marketing authorisation as last line therapy in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple proteases inhibitors.

User consultation
A readability test of the PL for Aptivus 100 mg/ml oral solution was performed. The composition of the test group is considered acceptable. The PL was initially evaluated in a pilot test which was performed with 5 participants, followed by two rounds of testing with 10 persons each. The pilot test led to a minor change in the PL. The change introduced between the pilot test and the main test was

provided by the MAH upon request. This amended PL was subject of the second and third round. No change was made in the PL, the layout or the questionnaire between the 1st and 2nd cycle test.

During the Readability User Test, at least 19 of 20 participants were able to find and understand the answer to each individual question, i.e. at least 90 % of the participants located the requested information of which at least 90 % showed that they were able to understand it. This is in line with the "Draft guideline on the readability of the label and package leaflet of medicinal products for human use" (Revision September 2006) Update of Directive 2001/83/EC as amended by Directive 2004/27/EC.

Results of the user test are therefore considered satisfactory and showed that the PL for Aptivus 100 mg/ml oral solution could be rated as readable and comprehensible according to the requirements.