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Product name: KALETRA
Procedure No. EMEA/H/C/368/X/27

SCIENTIFIC DISCUSSION

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1 INTRODUCTION

This is an application for an extension to the Marketing Authorisation (MA) for Kaletra (lopinavir/ritonavir) made pursuant to Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II (point 2 iii). The MAH would like to add a new pharmaceutical form and strength to the Marketing Authorisation (MA): Kaletra film-coated tablets 200 mg lopinavir/50 mg ritonavir.

Kaletra is currently the unique fixed boosted PI combination (including lopinavir + low dose ritonavir) available on the market. Given its antiviral potency, Kaletra is considered as a "gold standard" in the therapeutic management of HIV infected patients. However, its current daily dosing regimen is associated with particular constraints: a drug intake corresponding to 6 capsules per day, with food only, and requiring a refrigerated storage condition.

This new tablet formulation is aimed at simplifying the daily dosing regimen of Kaletra. The development of this new tablet formulation was mainly guided by the MAH's willingness of reducing the pill burden of lopinavir/ritonavir (from 6 (3 BID) soft gelatine capsules (SGC) daily to 4 (2 BID) tablets daily) and of avoiding the requirement of refrigerated storage condition.

Kaletra is indicated for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents. The recommended dosage in adults and adolescents is two tablets twice daily taken with food.

Overall, apart from the change in relation to the posology, interaction and pharmaceutical issues, the SPC information of the new formulation is comparable to the one of the currently marketed capsule formulation of Kaletra.

The MAH utilised melt-extrusion technology to develop new tablet formulation with a higher dose compared to the capsules and with improved stability at room temperature. Critical steps in the manufacturing process are identified and controlled. Control for intermediate and finished product is state of the art and validated according to relevant guidelines.

No new preclinical data has been provided with the exception of toxicity data on the main excipient: copovidone, a copolymer of vinyl pyrrolidone and vinyl acetate (60% / 40%).

Pharmacokinetics: Bioavailability studies were performed during formulation optimisation and bio-equivalency studies were done with the authorised capsules as comparator.

Pharmacokinetic studies were performed on compliance with GLP and GCP.

2 QUALITY ASPECTS

Introduction

Kaletra film-coated tablets contain 200 mg of lopinavir and 50 mg of ritonavir as active substance.

The other ingredients include:

- tablet core: copovidone, sorbitan laurate, colloidal anhydrous silica and sodium stearyl fumarate,
- film-coating: hypromellose, titanium dioxide, polyethylene glycol 400, hyroxypropyl cellulose, talc, silica colloidal anhydrous, polyethylene glycol 335, yellow ferric oxide (E172), polysorbate 80.

The tablets are packed into HDPE bottles with polypropylene caps or in PVC/fluoropolymer blisters.

Drug Substance

No change has been made to the active substances already authorised for Kaletra presentations (EU/1/01/172/01-03).

Lopinavir and ritonavir have very low water solubility.

Drug Product

- Pharmaceutical Development

This new film-coated tablet with a higher drug load (200 mg instead of 133.3 mg of lopinavir and 50 mg instead of 33.3 mg of ritonavir) has been developed to reduce the daily pill burden of the currently marketed soft capsule formulation (from 6 (3 BID) capsules daily to 4 (2 BID) tablets daily) and to avoid the requirement of refrigerated storage conditions.

The ratio of lopinavir to ritonavir in the formulation remains unchanged compared to the currently marketed formulations for Kaletra and their compatibility is supported by the already available stability data. The choice of excipients was based on physicochemical properties of the actives, processing consideration and results of pilot biostudies. Compatibility has been confirmed by development studies and by the finished product stability data. A safety assessment has been provided with regards to the level of copovidone used in the formulation (see non clinical section).

Formulation development has shown that lopinavir and ritonavir are uniformly dispersed in the matrix. The film coating is applied for taste and cosmetic purposes. The other excipients are added to facilitate processing and dissolution of the formulation in aqueous environments.

All the excipients are commonly used for oral formulations and they are all of PhEur quality except the film coating, which is satisfactorily controlled according to a different standard. Regarding the TSE risk, Kaletra does not contain any ingredient of ruminant origin.

Satisfactory specification has been provided for the HDPE bottles closed with polypropylene caps and for the PVC/fluoropolymer blisters.

The new film-coated tablet formulation appears to be suprabioavailable (around 20% increase of lopinavir and ritonavir PK exposure) compared to the currently marketed soft capsule formulation (see clinical section).

- Product Specification

The product specification includes tests controlled by validated methods for appearance, identity (HPLC and TLC), assay lopinavir (HPLC), assay ritonavir (HPLC), degradation products, dissolution, uniformity of dosage units lopinavir and ritonavir (PhEur), moisture and microbial limits (PhEur).
The related impurities of lopinavir and ritonavir are the same as the impurities for lopinavir and ritonavir except one specific degradation product of ritonavir, which is formed during the extrusion step of the manufacturing process. However, the process development and stability data along with qualification data support the proposed limits.
Due to the properties of the actives, correlation of the *in vitro* characteristics with *in vivo* performance was not assured and human pilot biostudies were used during development. The dissolution method appears capable of detecting the presence of undissolved ritonavir and lopinavir and suitable to ensure batch-to-batch consistency.
Batch analysis data provided for production scale batches comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the Product

Stability data have been provided for batches manufactured at the commercial manufacturing site and packed in HDPE bottles with polypropylene caps and in PVC/fluoropolymer blisters.
Under long term conditions (25°C/40% RH - commercial packaging) and accelerated conditions (40°C/75% RH - commercial packaging), respectively up to 18-month data and 6-month data have been provided.
The parameters tested included appearance, assay lopinavir, assay ritonavir, degradation products ritonavir, dissolution, moisture and microbial limits.
For all packaging and conditions no significant physical or chemical change was observed.
Photostability studies have shown that the finished product is non-light sensitive. Potential effect of moisture was tested at 25°C/40% RH, 25°C/50% RH, 25°C/60% RH and showed no detectable crystallisation of lopinavir and ritonavir.
The data provided support the proposed shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

No change has been made to the active substances lopinavir and ritonavir already authorised for Kaletra presentations (EU/1/01/172/01-03). This new pharmaceutical form allows to reduce the daily pill burden of the currently marketed soft capsule formulation and to avoid the requirement of refrigerated storage conditions. The excipients are commonly used for oral formulations and the packaging material is well documented. The manufacturing process enhances reproducibility of finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

3 NON-CLINICAL ASPECTS

Introduction

Results of pharmacological and toxicological studies of lopinavir and ritonavir were submitted and assessed with the original marketing authorisation application for Kaletra soft capsules and oral solution. The total adult daily dose for Kaletra film coated tablets is the same as for Kaletra soft capsules. No new non clinical safety issues have been associated with the tablets and therefore no additional preclinical data relating to the active substances has been submitted to support the use of the new formulation.

In regard to excipients and taking into consideration that the level of copovidone (main excipient) is higher than previously used according to US FDA Inactive Ingredient Listing, the MAH provided a package of toxicity studies performed by BASF Corporations and Knoll Pharmaceuticals.

Toxicology

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity studies for copovidone in rats and dogs have not shown specific findings up to the highest dosages administered, with sufficient safety margins. On a mg/kg basis, safety margins in rats and dogs were 65 and 51 times higher than the human exposure.

- Genotoxicity and Carcinogenicity

Copovidone was not mutagenic, nor carcinogenic in the performed studies.

Ecotoxicity/environmental risk assessment

Regarding the environmental aspects of Kaletra, for ritonavir, the PEC $_{surface\ water}$ was refined to 0.198 µg/l. The PEC/PNEC ratio for ritonavir = 0.132, thus <1 and does not require further investigations per the phase II Tier B evaluation. Consequently, ritonavir is unlikely to represent a risk to the environment.
However, for lopinavir, the PEC $_{surface\ water}$ was refined to 1.88 µg/L. The PEC $_{surface\ water}$ is greater than the limit of 0.01 µg/l proposed in the 2005 EMEA draft guidance. Concerning the estimation of the refined PEC/PNEC ratio, no data were available for the evaluation of lopinavir. An environmental risk assessment has not been adequately addressed by the MAH. Consequently, the MAH had to provide an environmental risk assessment for lopinavir according to the Note for Guidance on Environmental Risk Assessments for Pharmaceuticals (Draft CPMP/SWP/4447/00). Key environmental parameters were re-calculated using modelling software.

In order to model the fate of lopinavir in a sewage treatment plan (STP) with SimpleTreat (EUSES v 2.0.3) it was necessary to derive some modelled input parameters using the QSAR software EPIWIN V 3.01 (Syracuse Research Corporation).

The organic carbon adsorption coefficient (Koc) values calculated for these two molecules by EPIWIN were not used in any further modelling, as they were extremely high values. If an experimental value is available for the Kow, a more appropriate method of Koc estimation is by regression equations. This correlation method is the basis for the EUSES calculation in the absence of a user-defined value. It was decided therefore to conduct a sensitivity analysis with EUSES with respect to the Koc value. The Koc values used were: the value derived by EUSES based on the Kow of the compounds (2290 litre/kg and 2910 litre/kg for lopinavir and ritonavir, respectively); 2500 litre/kg (the highest Koc value for ritonavir, expressed to 2 significant figures); 5000 litre/kg; and 10000 litre/kg (the trigger value for terrestrial fate and effects assessment).

The PEC $_{surface\ water}$ values calculated for lopinavir after a treatment in a STP are less than 1.0×10^{-5} mg/litre (0,01 µg/litre).

Table 1:

Koc (kg/litre)	2290	2500	5000	10000
Untreated waste water (mg/litre)	1.88×10^{-4}	1.88×10^{-4}	1.88×10^{-4}	1.88×10^{-4}
STP effluent (mg/litre)	5.13×10^{-5}	5.06×10^{-5}	4.41×10^{-5}	3.66×10^{-5}
PEC SURFACE WATER (mg/litre)	5.11×10^{-6}	5.04×10^{-6}	4.38×10^{-6}	3.61×10^{-6}
PEC SEDIMENT (mg/kg wet weight)	2.58×10^{-4}	2.78×10^{-4}	4.79×10^{-4}	7.88×10^{-4}
PEC DRY SHWAGE SLUDGE (mg/kg)	8.53×10^{-2}	9.12×10^{-2}	1.47×10^{-1}	2.12×10^{-1}

The results of four short-term ecotoxicity studies were available for ritonavir. All of these studies had resulted in no observable effect on the test organism, at the maximum concentration of ritonavir used in the studies. The aquatic ecotoxicology of ritonavir was therefore modelled with ECOSAR V 0.99e and compared to these experimental results. ECOSAR V 0.99e predicts the ecotoxicity of a compound based on regression equations utilising their Kow values. The variability of the modelled data with the experimental data was similar to that due to experimental error. Ecotoxicology data for lopinavir were modelled with ECOSAR V 0.99e. The ecotoxicology data are shown in Table 4.

Table 2: Ecotoxicology data

All results are expressed as mg/litre

		Modelled Data [a]		Measured Data
Study Type		Lopinavir	Ritonavir	Ritonavir (NOEC)
Fish	14-day LC50	5.611	4.307	-
Fish	96-hr LC50	2.082	1.548	1.5
Fish	14-day LC50	5.611	4.307	-
Daphind	48-hr LC50	2.652	1.999	1.5
Green Algae	96-hr EC50	1.914	1.460	1.59
Fish	30-day ChV	0.401	0.308	-
Daphind	16-day EC50	0.406	0.334	-
Green Algae	96-hr ChV	0.812	0.695	-
Fish (SW)	96-hr LC50	1.598	1.309	-
Mysid Shrimp	96-hr LC50	0.101	0.065	-
Micro-organisms		-	-	5.0

- No value

a Values modelled with Syracuse EPIWIN Ver 3.01 based on SMILES notation

Risk characterisation ratios (RCR) were calculated for fish, daphnia and green algae based on the short term ecotoxicology data that were available for ritonavir and the equivalent modelled data for lopinavir. A conservative assessment factor of 1000 was used to calculate the predicted no effect concentrations (PNEC). The RCR values for each trophic level were calculated for each $PEC_{surface\ water}$ calculated by EUSES.

Table 3: Lopinavir

	RCR			
$PEC_{surface\ water}$ (mg/litre)	5.11×10^{-6}	5.04×10^{-6}	4.38×10^{-6}	3.61×10^{-6}
Daphnia [a]	1.93×10^{-3}	1.90×10^{-3}	1.65×10^{-3}	1.36×10^{-3}
Green algae [b]	2.67×10^{-3}	2.63×10^{-3}	2.29×10^{-3}	1.89×10^{-3}
Fish [c]	2.45×10^{-3}	2.42×10^{-3}	2.10×10^{-3}	1.73×10^{-3}
Micro-organisms [d]	-	-	-	-

All PNEC values were modelled with Syracuse ECOSAR V 0.99e and by applying an assessment factor of 1000 *ef* Table 4

a The PNEC for *Daphnia* was 2.652×10^{-3} mg/litre

b The PNEC for green algae was 1.914×10^{-3} mg/litre

c The PNEC for fish was 2.082×10^{-3} mg/litre

d No modelled data for micro-organisms available

Discussion on the non-clinical aspects

In response to the CHMP's request, $PEC_{surface\ water}$ of lopinavir had been re-calculated using modelling software and modelled physico-chemical values.

Consequentially, $PEC_{surface\ water}$ established using these modelled ecotoxicology data are not very reliable. Only the $PEC_{surface\ water}$ values determined on measured ecotoxicology data can be take into consideration ($PEC_{surface\ water}$ = 1,88 µg/l). However, this value exceeds the limit of 0.01 µg/l. No experimental studies have been performed. Instead the MAH provided ecotoxicology data modelled with a software (ECOSAR V 0.99e). The lowest value of modelled ecotoxicology data of lopinavir could be considered with regard to NOEC of ritonavir. The lowest modelled NOEC is 1.914 mg/litre in green algae. If a conservative factor of 1000 is used, the estimated $PNEC_{WATER}$ value is 1.914 µg/l. The $PEC_{surface\ water}$ / $PNEC_{WATER}$ ratio is below 1 and it could be considered that lopinavir is unlikely to represent a risk to the environment.

4 CLINICAL ASPECTS

Introduction

The clinical dossier is exclusively composed of pharmacokinetic studies performed in healthy volunteers.
All (M01-306, M01-381, M03-616, M04-703) except one study (M03-580) were performed at single dose.

- Study M01-306 aimed at determining the relative bioavailability of six pilot formulations of lopinavir/ritonavir tablets relative to the marketed soft gelatine capsule under non-fasting conditions,
- Study M01-381 aimed at determining the relative bioavailability of three pilot formulations of lopinavir/ritonavir tablets formulations chosen from study M01-306 relative to soft capsules formulations under fasting and non-fasting conditions.
- Study M03-616 (pivotal study) aimed at determining the bioavailability of the to-be-marketed tablet formulation manufactured at production scale relative to gelatine capsule. Fasting, moderate-fat and high fat conditions were also tested
- Study M04-703 (pivotal study) aimed at determining why different bioavailability results were found from studies M03-580 and M03-616 so determining the bioavailability of three different tablet lots (two were previously tested- lot 1 and pilot lot) compared to that of capsules.

- Study M03-580 had three main objectives:
    - To compare the single dose bioavailability of lopinavir/ritonavir 400/100 mg (1) as well as of lopinavir 800/200 mg (2) from a partial scale up lot of an experimental tablet formulation to that obtained from the capsule
    - To explore (multiple dose) the co-administration of the tablet formulation with a known CYP3A4 inducer, efavirenz (3). As a reminder the co-administration of efavirenz and Kaletra Capsule formulation justifying a dose increase from 400/100 to 533/133 mg daily.
    - Finally a meta-analysis was performed gathering the results of studies M03-616 and M04-703

GCP

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

Pharmacokinetics

- **Relative bioavailability between the to be marketed tablet formulation and the capsule formulation**

As detailed below for the pivotal studies, the results did not strictly match the criteria of bioequivalence across the studies. A supra-bioavailability of the tablet formulation as compared to the currently marketed formulation was consistently shown.

Study M03-616:

Results for lopinavir parameters:

Test vs. reference	Parameters	Standard CI 90%
Tablet moderate fat vs. SGC moderate fat	C_{max} AUC_{τ} AUC ∞	**1.230 – 1.362** **1.197 – 1.351** **1.195 – 1.348**
Tablet fasting vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	**1.314 – 1.615** **1.439 – 1.839** **1.431 – 1.824**
Tablet moderate fat vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	1.111 – 1.244 **1.191 – 1.352** **1.191 – 1.352**
SGC moderate fat vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	**1.191 – 1.470** **1.429 – 1.843** **1.425 – 1.831**
Tablet high-fat vs. Tablet moderate-fat	C_{max} AUC_{τ} AUC ∞	**0.780 – 0.913** 0.859 – 0.982 0.861 – 0.982
Tablet high-fat Vs Tablet fasting	C_{max} AUC_{τ} AUC ∞	0.877 – 1.124 **1.028 – 1.371** **1.029 – 1.373**

Results for ritonavir parameters:

Test vs. reference	Parameters	Standard CI 90%
Tablet moderate fat vs. SGC moderate fat	C_{max} AUC_{τ} AUC ∞	**1.286 – 1.517** **1.189 – 1.356** **1.177 – 1.336**
Tablet fasting vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	**1.495 – 1.950** **1.402 – 1.778** **1.376 – 1.706**
Tablet moderate fat vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	0.943 – 1.167 **1.066 - 1.253** 1.063 – 1.241
SGC moderate fat vs. SGC fasting	C_{max} AUC_{τ} AUC ∞	**1.112 – 1.480** **1.273 – 1.624** **1.256 – 1.567**
Tablet high-fat vs. Tablet moderate-fat	C_{max} AUC_{τ} AUC ∞	0.853 – 1.109 0.977 – 1.111 0.977 – 1.107
Tablet high-fat Vs Tablet fasting	C_{max} AUC_{τ} AUC ∞	**0.920 – 1.323** **1.071 – 1.453** **1.068 – 1.436**

Study M04-703:

Regimen tablet vs. SGC	Parameters	Standard CI 90%
Lopinavir		
Tablet lot A vs. SGC	C_{max} AUC_{τ} AUC ∞	**1.158 –1.300** 1.062 – 1.208 1.059 – 1.204
Tablet lot B vs. SGC	C_{max} AUC_{τ} AUC ∞	1.104 – 1.241 1.034 – 1.176 1.031 – 1..172
Tablet lot C	C_{max}	1.062 – 1.191

vs. SGC	AUC_τ AUC ∞	0.944 – 1.073 0.942 – 1.070
Ritonavir		
Tablet lot A vs. SGC	C_{max} AUC_τ AUC ∞	**1.242 – 1.530** 1.075 – 1.232 1.075 – 1.226
Tablet lot B vs. SGC	C_{max} AUC_τ AUC ∞	**1.163 – 1.433** 1.076 – 1.234 1.074 – 1.225
Tablet lot C vs. SGC	C_{max} AUC_τ AUC ∞	**1.044 – 1.283** 0.941 – 1.078 0.946 – 1.079

When the PK results related to the capsule derived from study M03-616 and M04-703 were compared, a slight difference was observed (around 10% in AUC), suggesting a variability in the PK of the capsule formulation used as reference in the bioequivalence studies with the tablet formulation. According to the MAH "this variability in the performance of the reference SGC alone may account for the difference in relative bioavailability assessment of the to-be-marketed tablet across studies". To solve this problem, the MAH has performed a meta-analysis [combining the two pivotal bioavailability studies (M03-616 and M04-703)] to better evaluate the relative bioavailability of the tablet as compared to the capsule formulation.

Results of meta-analysis combining data from the pivotal bioavailability studies (regimen A and C from study M03-616 and regimen A, B and D in study M04-703 are detailed thereafter:

Tablet vs.. capsule	**Parameters**	**Point estimate**	**Standard CI 90%**
Lopinavir			
Tablet vs. capsule	C_{max} AUC_τ AUC ∞	1.235 1.184 1.181	**1.188-1.285** 1.131-1.239 1.129-1.236
Ritonavir			
Tablet vs. capsule	C_{max} AUC_τ AUC ∞	1.349 1.202 1.193	**1.263-1.441** **1.146-1.261** 1.139-1.249

The results derived from this meta-analysis do not strictly match the criteria for bioequivalence between the tablet and capsule formulations. Again a higher bioavailability is observed with the tablet formulation as compared to the capsule formulation (around 20% higher exposure for lopinavir and ritonavir).

- **Food influence on the tablet formulation**

The food effect of the tablet formulation under fasting, moderate-fat and high-fat conditions was explored in the single dose study M03-616 in healthy volunteers.

Study	**Description** **Objectives**	**Study design**	**Population and Number**	**Treatment** **Dose (mg)**
M03-616	PK/Safety To assess the bioavailability of the new chosen tablet formulation (manufactured at production scale) compared to that of marketed capsules under fasting and non-fasting	Randomized Open-label Single dose Five periods	Healthy subjects 64 subjects planned 63 subjects completed	Regimen A: three 133.33/33.3 mg capsules following a moderate fat breakfast Regimen B: three 133.3/33.3 mg capsules under fasting conditions Regimen C: two 200/50 mg tablets (new) after a moderate-fat breakfast Regimen D: two 200/50 mg tablets (new) under fasting conditions

Study	Description Objectives	Study design	Population and Number	Treatment Dose (mg)
	conditions. The effect of food (high fat and moderate fat breakfast) on the tablet was also tested			Regimen E (5 subjects from each sequence who completed periods 1 to 4): two 200/50 mg tablets (new) after a high-fat breakfast. A wash out of 7 days separated the doses of each five study periods.

Based on the results of this study M03-616 it appears that the food influence is much more noticeable for the capsule (» 40% increase of the exposure) than for the tablet formulation (» 20% increase of the exposure). This justifies a capsule intake "with food only", whereas the to-be-marketed tablet formulation could be administered "with or without food".
Moreover, when considering the relative bioavailability between the tablet and capsule formulation under fast and fed conditions:

- Under fed conditions (C/A) a supra-bioavailability of the tablet formulation is observed as compared to the capsule formulation.
- This supra-bioavailability is even more noticeable under fasting (D/B) conditions (likely in relation with the sub-optimal conditions of drug intake for the capsule formulation which is only to be administered with food).

- **Exploration of the co-administration with a CYP3A4 antiretroviral inducer, efavirenz**

A specific part of study M03-580 was performed at multiple dose and was aimed at exploring the co-administration of Kaletra tablet formulation with efavirenz, according to the following schema:
- From day 8 to day 18: lopinavir/ritonavir 400/100 mg bid.
- From day 18 to day 21: lopinavir/ritonavir 400/100 mg bid + efavirenz 600 mg od.
- From day 22 to day 32: lopinavir/ritonavir 600/150 mg bid + efavirenz 600 mg od.

Samples were collected on day 18 and 32 during a 12h-dosing interval.

The results are detailed thereafter:

Test vs. reference	Parameters	Standard CI 90%
Lopinavir		
Tablet + efavirenz vs. tablet alone	C_{max}	**1.275-1.442**
	C_{min}	**1.207-1.444**
	$C_{through}$	**1.256-1.477**
	AUC 12	**1.284-1.435**
Ritonavir		
Tablet + efavirenz vs. tablet alone	C_{max}	**1.678-2.199**
	C_{min}	**1.405-1.742**
	$C_{through}$	**1.399-1.840**
	AUC 12	**1.620-1.952**

Given the strength of the to-be-marketed tablet formulation (200/50 mg lopinavir/ritonavir), the MAH proposed a dose increase from 400/100 mg (2 tablets) BID to 600/150 mg (3 tablets) BID with the tablet to mimic the dose increase currently recommended with the capsule [from 400/100 (3 capsules) BID to 533/133 mg (4 capsules) BID]. However, such a dose increase for the tablet obviously leads to major increase of the lopinavir and ritonavir PK exposures (56 to 92% higher than the capsule exposure). As a second step, based on a modelling program the MAH concludes that a dose increase of Kaletra when co-administered with efavirenz is no longer necessary when Kaletra is used as a tablet formulation. This conclusion is even extended to the co-administration of other antiretroviral agents that currently requires a dose adjustment (increase) with the capsule formulation (nelfinavir, amprenavir).

The result of a study performed in healthy volunteers together with extrapolation, is not sufficient to ensure a safe co-administration of efavirenz (as well as nelfinavir and amprenavir) with the new tablet formulation of Kaletra. The co-administration of efavirenz without any dose increases of Kaletra tablets, as currently proposed by the MAH, needs to be explored within a specific pharmacokinetic study to validate the MAH's assumption. Moreover, such a confirmatory study needs to be performed in the target population of HIV infected patients to provide a reliable demonstration of the pharmacokinetics of this new formulation. Therefore, the MAH was requested to provide the results of a pharmacokinetic interaction study in healthy volunteers to further assess the co-administration of Kaletra tablet and efavirenz.

New pharmacokinetic interaction study between Kaletra tablet and efavirenz in healthy volunteers M05-792

Study M05-792 is a Phase 1, multiple-dose, non-fasting, open-label study assessing the pharmacokinetics and safety of lopinavir/ritonavir (LPV/r) 400/100 mg dosed twice daily (BID) as the tablet formulation co-administered with efavirenz (EFV) 600 mg (tablet) every evening (QHS) compared to lopinavir/ritonavir 400/100 mg BID dosed as the soft gelatine capsule (SGC) in healthy adults.

Although the ritonavir pharmacokinetic parameters are not significantly influenced by the co-administration with efavirenz, the same does not apply for lopinavir. Indeed, all pharmacokinetic parameters of lopinavir with efavirenz are markedly below (up to 42% of the C_{min} value) those obtained with the capsule administered alone. Exposure of lopinavir tablet combined with efavirenz will be lower than that obtained with lopinavir capsule or lopinavir capsule 533/133 mg with efavirenz. Co-administration of Kaletra tablet at unchanged dose with efavirenz will expose patients to suboptimal exposure to Kaletra with potential risk of emergence of resistance.

It is noteworthy that when Kaletra capsule is combined with efavirenz, the lopinavir C_{min} is decreased to around 45% and the C_{trough} to around 35% as compared to the Kaletra capsule recommended 400/100 mg BID dose. Based on these data the MAH has recommended that the dose of Kaletra should be increased from 400/100 mg BID to 533/133 mg BID. However, when Kaletra tablet is combined with efavirenz, the lopinavir C_{min} is decreased to around 40% and the C_{trough} to around 30% as compared to the Kaletra tablet recommended 400/100 mg BID dose. However, in this case the MAH is confident that there is no need for any Kaletra dose increase and that no clinical consequence is expected.

This leads to serious doubts about the claimed lack of clinical consequence of decreased C_{min} and C_{trough} exposure:
Given that the Kaletra tablet dossier only consists of pharmacokinetic data (i.e. no clinical data is available with the tablet formulation of Kaletra), there is a need to stick to the PK parameters of the Kaletra capsule whose MA has been granted on the basis of a valid efficacy/safety demonstration.

The selected dose of Kaletra capsule corresponds to specific values of PK parameters. This selected dose has been clinically validated based on a reliable pivotal study. In spite of this, the MAH claims that due to the supra-bioavailability of the tablet formulation, conclusions on the interaction of the capsule formulation (i.e. the need to administer a higher dosage of Kaletra to patients) with efavirenz do not apply to the tablet formulation. However, such reasoning on one issue could lead to doubts about the validity of the recommended dose for the tablet formulation, which in all other instances is based upon the dose finding studies for Kaletra capsules. If a lack of clinical consequence associated with a marked decrease in C_{min}/C_{trough} could indeed be assumed by the MAH, why then did he not propose an overall lowering of the recommended dose for the tablet formulation.

It has to be emphasised that there is a particular need to stick to the PK parameters corresponding to the selected dose that has been substantiated by reliable pivotal studies (M98-863 notably). Otherwise, there could be potential consequences in terms of time to virological failure and of risk of emerging resistance associated with sub-optimal lopinavir levels.

Finally the MAH considers that there is no need to confirm the results of the interaction study derived from healthy volunteers in HIV infected patients, since the PK parameters are expected to be quite close in both populations.
In this respect, it is important to emphasise that lopinavir concentrations after administration of capsules seem to be lower in patients compared to healthy volunteers. Such effect might also be observed with Kaletra tablets:

		SGC400/100 alone		SGC400/100 +efavirenz	
		M97-741(Healthy V)	M97-720(HIV)	M97-741(HealhyV)	M98-957(HIV)
AUC0-12	µg.h/ml	103 ±28	83±44	85± 22	62±26
Cmin	µg/ml	6.0± 2.3	**3.8**±3.4	3.7± 1.6	**2.2**±1.6
Ctrough	µg/ml	6.9± 2.1	**5.5**±4.0	5.0± 1.8	**3.7**±2.6

Overall, contrarily to the MAH's conclusion that there is no need for Kaletra dose increase when Kaletra tablet is combined with efavirenz (i.e. different attitude as the one recommended for the capsule: dose increase from 400/100 mg BID to 533/133 mg BID), the CHMP considers that the interaction study results reinforce the CHMP's concern that this co-administration without dose adjustment will expose patients to sub-optimal concentrations and potential risk of emergence of resistance.
Given that the unique dose adjustment explored by the MAH with the tablet (i.e. 600/150 to mimic the 533/133 mg dose increase recommended with the capsule) was associated with an overexposure (up 56% for lopinavir and 92% for ritonavir) the MAH is requested to further explore a dose increase of Kaletra tablet when combined with efavirenz (e.g. by providing an half-dose tablet of 100/25 mg to be added to Kaletra 400/100 mg BID).
In the meantime the CHMP recommends that this co-administration should be not recommended for the lopinavir/ritonavir 400/100 mg BID regimen. However, if judged clinically necessary prescribers have the possibility to co-administrate lopinavir/ritonavir 600/150 mg and efavirenz. However, given the overexposure associated with the co-administration of lopinavir/ritonavir 600/150 mg BID with efavirenz 600 mg once daily, prescribers will have to closely monitor safety aspects of this co-administration.

The same should apply for nelfinavir, amprenavir and nevirapine (since an extrapolation has been made for Kaletra capsule between the recommendation for efavirenz and these other antiretroviral agents).

Pharmacodynamics

No new data on pharmacodynamics of Kaletra tablet formulation have been submitted within this application.

Clinical efficacy

No new data on clinical efficacy of Kaletra tablet formulation have been submitted within this application.

Clinical safety

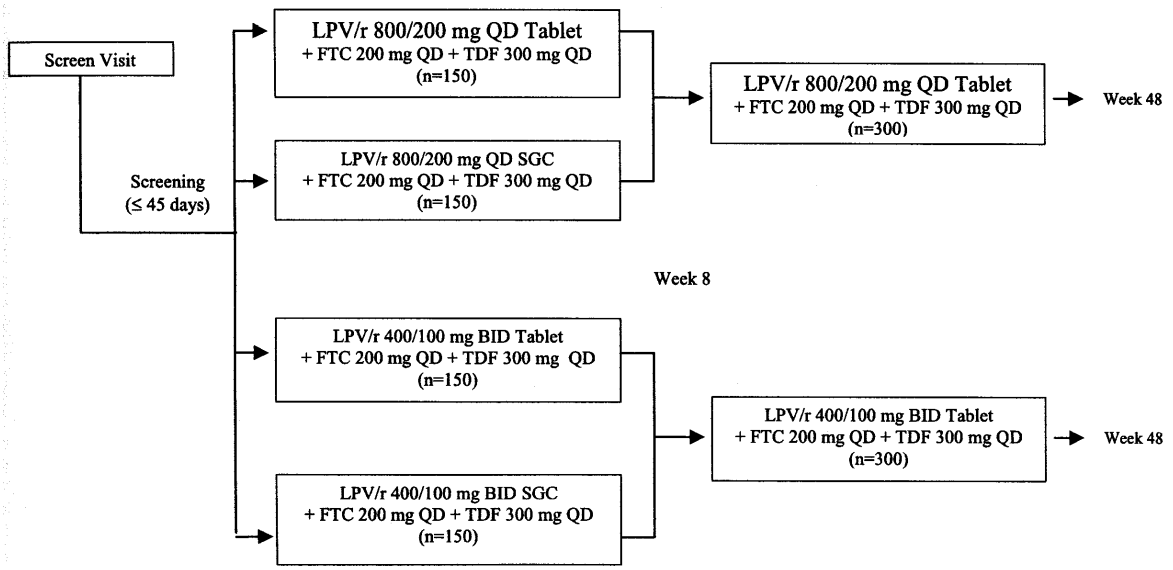
In response to the CHMP request for providing comparative safety data between the capsule and tablet formulation of Kaletra in the target population of HIV infected patients, the MAH has proposed to derive such data from a recently initiated study M05-730:
M05-730 study is an open-label, randomized, multiple centre, multi-country study designed to compare the safety and tolerability of lopinavir/ritonavir tablets versus soft gel capsules, and to compare the safety, tolerability and antiviral activity of lopinavir/ritonavir tablets when dosed QD versus BID in combination with nucleoside reverse transcriptase inhibitors in the treatment of antiretroviral naïve, HIV-1 infected subjects. This study plans to enrol 600 patients.

The primary efficacy variable will be the proportion of subjects with plasma HIV-1 RNA levels below 50 copies/ml at Week 48 (to compare BID and QD dosing tablet regimens) .

The primary safety variable will be the proportion of subjects with adverse events of diarrhoea during the first 8 weeks of study drug treatment (tablet or SGC formulation).

It is important to note that this study is also expected to provide useful pharmacokinetic comparative data between the capsule and tablet formulations in HIV infected patients. Indeed, approximately 20 subjects per treatment arm (80 subjects total) will have full 12 or 24 hour (depending on lopinavir/ritonavir dosing interval) pharmacokinetic analysis performed at Week 2. In addition, patients who initiate therapy with the SGC formulation will have repeat pharmacokinetic analysis performed at Week 10, approximately 2 weeks after switching from the SGC to the tablet formulation.

The study design is detailed thereafter:



NOTE: Co-formulated emtricitabine and tenofovir disoproxil fumarate will be used where available. Where emtricitabine is not available lamivudine 300 mg QD will be substituted.

Even if the main objective of the proposed study M05-730 is to validate a QD regimen of the tablet, the first part of the study is of particular interest for providing comparative PK and short term safety data (gastrointestinal AEs) between the capsule and the tablet formulations in the target population of HIV infected patients, in line with the CHMP request. As a matter of fact, this request was not considered as a prerequisite for the MA of Kaletra tablets by the CHMP but rather as a post approval commitment.
Nevertheless, it should be stated that without the initiation of this study prior to the approval it would have been quite difficult to enrol patients in the capsule arm with the tablet formulation already approved. Therefore, it is very useful that this study has already started because otherwise the possibility of obtaining these comparative PK and safety data would have been significantly compromised. Finally, it is unfortunate that this study is not blinded. Nevertheless, this seems acceptable given the pill burden needed for a blinding design.

Overall, this study represents the most critical aspect of the proposed risk management programme.

Another issue to consider is the potential for medication errors, resulting from the temporary co-existence on the market of the capsule (requiring the ingestion of 6 capsules per day) and tablet (allowing a reduction to 4 tablets per day, with a different interaction profile and different storage condition) formulations. The MAH indeed considers that there is a need for transition period from SGCs to tablets ranging from 6 to 12 months.

If the need for a transition period is supported its time duration should be minimal. In this field the MAH has to justify the 6-12 months delay for the substitution. Moreover, the release of the tablet

formulation on the market will have to be accompanied by a letter to health care professionals to avoid any medication errors. The MAH is requested to provide a proposal in this field.
These two questions have been addressed to the MAH during the assessment process. The MAH answered that with the support of the CHMP, he commits that local affiliates in each EU country will work closely with the national agencies to define a plan and determine timelines appropriate for transition from Kaletra soft capsules to the tablet formulation in their local markets. Coordination with national agencies will be key to identifying a definitive launch date to initiate advanced planning that will facilitate an expedited transition timeline. Furthermore, the proposed Dear Health Care Professional Letter (see Annex 6) will be revised to more clearly identify the risk for medication errors during the transition period. The importance of the local transition plan will also be highlighted in this letter. The final DHCPL will be submitted for CHMP review prior to first product launch in the EU.
The MAH's responses could be considered as endorsed. It is admitted that the transition period might vary across Member States. . A revised proposal will have to be proposed by the MAH for validation before the release.

- **Paediatric population**

The replacement of the capsule formulation by the tablet formulation will lead to a gap between the actual large availability of Kaletra SGC in children (children with 0.4<BSA<1.75 may resort with soft capsule) and the limited availability of the new Kaletra tablet in children (the available 200/50mg tablet is only suitable for children with BSA greater than 1.3m2), as reflected in the table below:

Body Surface Area* (m^2)	**Twice Daily Oral Solution Dose (230/57.5 mg/m^2)**	**Twice Daily Soft Capsule Dose**	**Twice daily tablets**
0.25	0.7 ml (57.5/14.4 mg)	NA	NA
0.40	1.2 ml (96/24 mg)	1 soft capsule (133.33/33.3mg)	NA
0.50	1.4 ml (115/28.8 mg)	1 soft capsule (133.33/33.3mg)	NA
0.75	2.2 ml (172.5/43.1 mg)	1 soft capsule (133.33/33.3mg)	NA
0.80	2.3 ml (184/46 mg)	2 soft capsules (266.6/66.6mg)	NA
1.00	2.9 ml (230/57.5 mg)	2 soft capsules (266.6/66.6mg)	NA
1.25	3.6 ml (287.5/71.9 mg)	2 soft capsules (266.6/66.6mg)	NA
1.3	3.7 ml (299/74.75 mg)	2 soft capsules (266.6/66.6mg)	NA
1.4	4.0 ml (322/80.5 mg)	3 soft capsules (400/100mg)	2 tablets (400/100mg)
1.5	4.3 ml (345/86.3 mg)	3 soft capsules (400/100mg)	2 tablets (400/100mg)
1.75	5 ml (402.5/100.6 mg)	3 soft capsules (400/100mg)	2 tablets (400/100mg)

Therefore, the development of a reduced-strength paediatric tablet, which would allow to supply children with BSA >0.8 m2 with a tablet formulation and reduce the gap between availability of the old and new oral solid formulation, is particularly awaited in this field.

The MAH explored dosing of paediatric patients with the tablet formulation. Although the MAH continues to endorse the use of lopinavir/ritonavir oral solution as the most appropriate formulation, allowing precise dosing, in paediatric patients, the MAH, recognising that some patients may prefer the tablet over the oral solution. The MAH has therefore committed himself to the development of a paediatric tablet strength.

5 PHARMACOVIGILANCE

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures post approval.

A detailed description of the Company's pharmacovigilance system including the responsibilities of the EU qualified person, the organisation, the system for collecting adverse events, the database in which the adverse events are contained, and the processes surrounding signal detection, co-licensing agreements, quality management, quality assurance, compliance, and training was provided by the MAH.

- **EU qualified person for pharmacovigilance**

Only the job description of the qualified person is provided by the MAH.
The following data are lacking and should be provided:
- The name, address, contact details of the Qualified Person responsible for pharmacovigilance, located in the EEA.
- The Curriculum Vitae of the qualified person responsible for pharmacovigilance and a description of the back-up procedure to apply in his absence, including the information relevant to their role (qualifications, training and experience). The qualified person should be able to justify an experience in pharmacovigilance.

- **Organisation**

The organisation chart for global pharmacovigilance is presented and the relationships between the pharmacovigilance units are illustrated. The CHMP welcomes the brief summary of the pharmacovigilance activities undertaken by each of the units involved. However, pharmacovigilance procedures in place are not presented in this report. A list of the written policies and procedures describing the pharmacovigilance activities of the company should be provided. These need not be separate titles but the list should indicate which procedures cover activities. Copies of the procedures should be available within two working days on request by the Competent Authorities. All information received by the MAH should be managed in order to respect the confidentiality of patients and reporters.

The MAH should provide a flow diagram indicating the flow of safety reports of different origins and types obtained and transmitted. These should indicate how reports/information is processed and reported from the source to the point of receipt by the Competent Authorities and, where appropriate, to healthcare providers.

- **Adverse event database**

The MAH is using a global electronic system for storing and reporting adverse events. The MAH should clarify if this database is compliant with ICH E2BM and if the updated version of MedDRA 9.0 is used (internationally agreed standard for electronic submission of adverse reaction reports).

- **Co-licensing agreements**

The MAH has a system in place to assure that the EU qualified person is aware of the details of any pharmacovigilance safety data exchange agreement for products marketed in the EU.
The MAH should provide a brief description of the agreements with co-marketing partners and contractors for pharmacovigilance activities, including reporting responsibilities and arrangements for literature searches.

- **Quality Management**

Global Pharmaceutical Research & Development (GPRD) management, in conjunction with GDRD QA management, provides an organisational structure that assures work is conducted in accordance with the Quality system. GPRD QA maintains the Quality System and conducts quality audits.
The CHMP agrees with the brief description of the quality management system. The MAH also presented the Quality Assurance support for the Abbott pharmacovigilance system provided by the global audit program. Particular emphasis is placed on organisational roles and responsibilities for the activities and documentation and for ensuring corrective and preventive action.

- **Compliance**

This information is analysed to identify opportunities to improve and enhance existing reporting related procedures and processes. Pharmacovigilance compliance metrics are compiled on a monthly basis. Metrics are provided related to the EMEA and Affiliate local regulatory reporting requirements. Individual case reporting metrics are obtained and analysed. Formal investigations into any instances of non-compliance are initiated whenever appropriate. Senior management is informed of compliance metrics at regular intervals and provides recommendations to continually improve the monitoring process.

- **Training**

The MAH is committed to ensuring staff are trained to the highest standards therefore Global Pharmacovigilance has a team dedicated to training. This active team provides training through a variety of media and ensures that all training activities are appropriately documented and recorded in personal training files. Training matrices have been developed for all roles to ensure that staff receives both initial and maintenance training in all relevant areas. Each year a regional pharmacovigilance training meeting is conducted for all affiliates including those within the Europe.
While the CHMP agrees with the brief description of the training system but the MAH should indicate where the training records, CVs and job descriptions can be found.

In conclusion, the MAH's pharmacovigilance system is globally endorsed. However, some further data should be provided in the setting of a follow-up measure to be provided as a post-approval commitment in order to fully match the pharmacovigilance regulatory obligations (see 2.6 of this assessment report).

Risk Management Plan

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potentially different safety profile for the tablet formulation due to supra-bioavailability	Return to 6-month periodicity for PSURs.	
	Conduct of a phase III study that will provide a comparative assessment of the tablet tolerability profile relative to the SGC in 600 HIV infected patients (study M05-730).	
Potential medication error due to temporary co-existence of capsule and tablet formulation on the market.	The MAH commits to work closely with each national agency to define a plan and determine timelines appropriate for transitions from Kaletra soft capsules to the tablet formulation in each local market. Coordination with national agencies will be key to identifying a definitive launce date to initiate advanced planning that will facilitate an expedited transition timeline.	Revised Dear Health Care Professional Letter (DHCPL, see Annex 6 to this Assessment Report) to be submitted to the CHMP for endorsement prior to first product launch in the EU. The MAH will work closely with each national competent authority to ensure that prior to launch in each Member State, health care professionals are provided with the DHCPL informing them about the possibility of confusion and dosage errors due to the impending co-existence of both pharmaceutical forms (soft gel capsule and film-coated tablets).

The CHMP, having considered the data submitted in the application, is of the opinion that the above mentioned risk minimisation activities are necessary for the safe and effective use of the medicinal product.

The two main concerns in regard to the tablet formulation are first the potentially different safety profile for the tablet formulation due to supra-bioavailability. Second the potential for medication errors due to temporary co-existence of capsule and tablet formulation on the market, each of them following a different posology.

In this regard, the MAH states that his risk minimisation efforts for the introduction and continued surveillance of Kaletra tablets described in this response are comprehensive enough to ensure patient safety. Key components of the overall safety surveillance plan include continued pharmacovigilance monitoring and reporting of safety findings in PSUR submissions, a return to 6-month periodicity for PSURs, additional efforts to minimise the risk of patient confusion and associated medication errors during the 6-12 month transition period (including product packaging and patient, prescriber and pharmacist education), and the conduct of a phase III study, which will provide a comparative assessment of the tablet tolerability profile relative to the SGC in 600 HIV infected patients.

With regards to the potential for medication errors, this potential risk will be anticipated with several steps as already applied in the USA, and will help to minimise the risk of medication errors:

- Educational material for patients, especially with description on key differences between capsules and tablets, and guidance on switching to the new formulation
- Educational material for pharmacists and doctors
- A short transition period from capsules to tablets, ranging from 6 to 12 months
- A different colour for tablets compared to capsules (yellow versus orange)
- A different colour for the product packaging (yellow) with two yellow tablets displayed in bottom left corner of the label.

The MAH presented again in an extensive way the arguments advanced in the initial application, including a similar drug exposure in multiple dose studies across both formulations and between healthy and HIV-1 infected subjects, a potential even better safety profile of the tablet compared to the capsule. These arguments were judged as not convincing enough to reassure the safety profile of the tablet formulation (see consolidated list of questions, Annex 3). In particular, given that the clinical dossier of the Kaletra tablet formulation only consists of pharmacokinetic data performed in a limited number of healthy volunteers almost exclusively in single dose, it is inappropriate to draw any conclusion at this stage on the safety profile of this tablet formulation, especially in comparison to the capsule formulation.

As a matter of fact, the more valuable information with regard to the safety profile of the tablet formulation will be issued from the ongoing Phase III study, study M05-730, allowing to provide comparative safety and PK data between tablet and capsule formulations in the targeted population of HIV infected patients (see detailed design and discussion on this study in question 11 below). This open-label study, initiated in December 2005, plans to include 600 naïve HIV-infected patients.

Another issue to consider is the potential for medication errors, resulting from the temporary co-existence on the market of the capsule (requiring the ingestion of 6 capsules per day) and tablet (allowing a reduction to 4 tablets per day, with a different interaction profile and different storage condition) formulations. The MAH states that there is a need for transition period from SGCs to tablets ranging from 6 to 12 months.

The CHMP considers that this transition period should be minimal but it is acknowledged that this duration might vary within European Member States. This will have to be discussed at a national level. Moreover, the release of the tablet formulation on the market will have to be accompanied by a letter to health care professionals to avoid any medication errors. This has been added to the post approval commitments as laid down in the Letter of Undertaking.

6 OVERALL CONCLUSIONS, RISK/BENEFIT ASSESSMENT AND RECOMMENDATION

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

No new non-clinical data in regards to safety issues of the active substances were submitted. The submitted data for the repeat dose toxicity for copovidone showed no specific findings up to the highest dosage administered and were therefore judged satisfactory. The remaining concern relates to conflicting data for the active substances in regards to ecotoxicity about discrepancies between modelled values and measured values of water solubility at 25°C needs further clarification. The MAH should explain these discrepancies and justify the validity of the data used in the software.

Pharmacokinetics

The clinical dossier was exclusively composed of pharmacokinetic studies performed in healthy volunteers. Results of meta-analysis combining data from the pivotal bioavailability studies (regimen A and C from study M03-616 and regimen A, B and D in study M04-703) showed that the criteria for bioequivalence were not strictly met. A 20% higher exposure for lopinavir and ritonavir with the tablet formulation as compared to the tablet can be observed. As the food effect is more expressed with the capsule formulation, this supra-bioavailability is even more noticeable under fasting conditions than under fed conditions. Exploration of the co-administration with a CYP3A4 antiretroviral inducer (efavirenz) showed a need to increase the dosage for Kaletra tablet when given concomitantly with these medicinal products. The SPC was updated accordingly.

Safety

No apparent deterioration of the safety profile is observed with the tablet as compared to the capsule formulation of Kaletra. However, the safety analysis has important limitations since it is based on studies performed in healthy volunteers and at single dose as well as on historical data. Therefore, the safety data cannot be regarded as strictly reassuring in regards to the potential alteration of the safety profile associated with the apparent supra-bioavailability of the tablet as compared to the capsule formulation of Kaletra (around 20% increase of lopinavir and ritonavir PK exposures). This question will be addressed by the findings of a study comparing the capsule formulation with the new tablet formulation in HIV infected patients that has been initiated by the MAH.

For paediatric patients, the tablet formulation does not provide the optimal flexibility to best support accurate dosing. The continued availability of lopinavir/ritonavir oral solution, with its inherently greater dosing flexibility remains the preferred formulation for use in the paediatric population. However, the fact that an available solid oral form will no longer be available for children with BSA of less than 1.3 m^2 in view of the replacement of the capsule formulation by the tablet formulation will create difficulties in clinical practice. Therefore, the MAH is required to explore the development of a dosage that will allow a finer dose titration in this population for a solid pharmaceutical form.

Overall, provided that no concern on the safety profile of the tablet formulation with its supra-bioavailability emerges from the ongoing study M05-730, routine pharmacovigilance activities, including continued pharmacovigilance monitoring and reporting of safety findings in PSUR submissions, as well as a return to 6-month periodicity for PSURs are considered to be adequate to detect any new signals associated with the new tablet formulation. Additional efforts to minimise the risk of patient confusion and associated medication errors during the transition period (including product packaging and patient, prescriber and pharmacist education) are judged adequate by the CHMP.

Risk-benefit assessment

This new tablet formulation of Kaletra presents advantages over the currently marketed capsule formulation that it is ultimately expected to replace: in particular a reduced pill burden (from 3 BID to 2BID) and no need for refrigerated storage conditions.

The MAH has submitted a limited dossier to support the Marketing Authorisation of this new formulation.

In effect, the clinical dossier consists exclusively of pharmacokinetic studies performed in healthy volunteers at single dose (except one study at multiple dose). No data in HIV infected patients is available. This is particularly critical since the demonstration of bioequivalence is quite disputable. As a matter of fact, a supra-bioavailability of the new formulation is observed (increase of around 20% of the lopinavir and ritonavir exposures) with a potential impact on the safety profile of this fixed combination. It cannot be excluded that the difference be more marked in HIV infected patients. Moreover, given this supra-bioavailability the MAH considers that the recommended dose increase of Kaletra when combined with efavirenz, should only apply for the capsule formulation but is no longer necessary for the tablet formulation. However, this assumption was only based on modelled data that suffered from limitations.

Therefore, at the D120 list of questions the MAH was requested to address two main issues:

- First, to make a proposal for collecting reassuring comparative PK and safety data between the capsule and tablet formulation in the target population of HIV infected patients.

The MAH has just initiated (December 2005) a new open label study (M 05-730) in antiretroviral naïve patients (n=600) whose main objective of this study is to validate the QD regimen of the tablet formulation. Nevertheless this study is de facto expected to provide comparative pharmacokinetic data

as well as short term (8 weeks) gastrointestinal safety data (diarrhoea) between the capsule and tablet formulation.

- Second, to provide the results of an interaction study between Kaletra tablet formulation and efavirenz in healthy volunteers.

In line with the CHMP request, the MAH has provided the results of a new interaction study (M05-792) with efavirenz. However, contrarily to the MAH's conclusion that there is no need for Kaletra dose increase when Kaletra tablet is combined with efavirenz (i.e. different recommendation as the for the SGC: dose increase from 400/100 mg BID to 533/133 mg BID), the CHMP considers that the interaction study results [reduced C_{trough} (27%) and C_{min} (42%)] reinforce the CHMP concern that this co-administration without dose adjustment will expose patients to sub-optimal concentrations and potential risk of emergence of resistance.
Given that the unique dose adjustment explored by the MAH with the tablet (i.e. 600/150 to mimic the 533/133 mg dose increase recommended with the capsule) was associated with an over-exposure (up 56% for lopinavir and 92% for ritonavir) the MAH is requested to further explore a dose increase of Kaletra tablet when combined with efavirenz (e.g. by providing an half-dose tablet of 100/25 mg to be added to Kaletra 400/100 mg BID).
In the meantime, the CHMP considers that this co-administration should be discouraged. As a matter of fact, stating that this co-administration is not recommended is not expected to significantly hamper the therapeutic management of patients, since the resort to this co-administration is expected to be marginal in clinical practice especially in antiretroviral naïve patients but also in antiretroviral experienced patients. Nevertheless, this is not a formal contra-indication, i.e. if judged necessary prescribers still have the possibility to co-administrate lopinavir/ritonavir 600/150 mg and efavirenz 600 mg QD, while closely monitoring safety aspects of this co-administration.
The same should apply for nelfinavir, amprenavir and nevirapine (since an extrapolation has been made for Kaletra capsule between the attitude recommended with efavirenz and with these other antiretroviral agents).

Overall, the CHMP considers that the benefit risk balance of Kaletra new tablet formulation is favourable. This new tablet formulation can be approved with the MAH's committement to a list of follow-up measures.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and additional risk minimisation activities were required.

7 RECOMMENDATION

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Kaletra film-coated tablets in the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents was favourable and therefore recommended the granting of the marketing authorisation.