1. SCIENTIFIC DISCUSSION

1.1 Introduction

A Community Marketing Authorisation for the HIV protease inhibitor, saquinavir (Invirase), hard capsule (HC) formulation was granted by the European commission on 04 October 1996 for the treatment of HIV-1 infected adults. This was followed by the Marketing Authorisation of Fortovase, a soft gel capsule formulation (1998).

Saquinavir, when given alone, has a very low systemic bioavailability. This is a function of incomplete absorption and high first pass metabolism mediated via cytochrome p450 3A4 (CYP3A4) in the gut and liver. Absorption is enhanced by dose administration with food. The proportion of the dose extracted by first pass metabolism can be reduced by CYP3A4 inhibition. Grapefruit juice, which inhibits the activity of CYP3A4 in the gut wall, increases systemic bioavailability by ~1.5-2 fold; however concomitant administration of other, more potent, inhibitors of hepatic CYP3A4 increases saquinavir bioavailability more substantively in a manner which is dependent on the relative potency of CYP3A4 inhibition. This feature of the pharmacology of saquinavir has been exploited by giving it concomitantly with ritonavir, a potent time dependent inhibitor of CYP3A4, to "boost" saquinavir exposures – in this case by ~ 10 fold, relative to monotherapy**.** The approved "boosted" combination regimen is 1000 mg Invirase given in combination with 100 mg ritonavir twice daily. This regimen is now an established part of therapy for HIV infection.

With the present 200 mg capsule strength, this dose regimen requires a total of 5 saquinavir capsules and one ritonavir capsule per dose (a total of 12 daily). The Marketing Authorisation Holder (MAH) has now developed a 500mg saquinavir film coated tablet (FCT) and seeks to introduce this to the market. Pursuant to Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II, point 2, indent (iii), Roche applied with the present application to add this new strength, i.e. 500 mg film coated tablets in order to further improve dosing convenience. This reduction in pill count is highly likely to result in improved compliance and thereby represents an improvement over the present Invirase HC dose form.

1.2 Quality aspects

Introduction

Invirase is presented as film-coated tablets containing 571.5 mg of saquinavir mesylate equivalent to 500 mg of saquinavir.

The other ingredients include:

- tablet core: povidone, lactose monohydrate, croscarmellose sodium, microcrystalline cellulose and magnesium stearate,
- tablet film-coating: hypromellose, titanium dioxide (E171), talc, iron oxide yellow and red (E172) and glycerol triacetate.

The tablets are packed in a HPDE bottle with a tamper evident screw closure.

Drug Substance

Saquinavir is the active substance of the centrally authorised medicinal product Invirase 200 mg hard capsules (EU/1/96/02/001) to which no change has been made. It is characterised by a low solubility, a low bioavailability (approximately 4 %) and a bitter taste. Batch analysis data provided for 5 recent production batches comply with the authorised specifications.

Drug Product

- Pharmaceutical Development

This new pharmaceutical form has been developed in order to support patient adherence to treatment by reducing daily pill burden (from 5x200 mg hard capsules 2 times a day to 2x500 mg tablets 2 times a day). A film-coated tablet is a well-accepted pharmaceutical form for oral administration.
As previously, the formulation is optimised by the use of the mesylate salt and by micronisation of the active substance. The function of each excipient and the rationale for its use has been satisfactorily described. The film coat provides taste masking and assists patient swallowing. All the excipients selected are of PhEur quality and the colorants iron oxide yellow and red comply with EU requirements. Regarding the TSE risk, the lactose monohydrate prepared from milk of bovine origin has been considered in compliance with the current TSE requirements. The magnesium stearate and the glycerol triacetate are from vegetable origin.
The primary packaging selected is of PhEur quality.

Two formulations differing only in the composition of the film coat were used in clinical studies. The initial formulation manufactured at a development site was used in study BP17058, whereas the proposed commercial formulation manufactured at the commercial manufacturing site was used in study BP17359 and study BP17653. Dissolution profiles for these batches show rapid dissolution, demonstrating that tablet dissolution is independent of film coat composition and manufacturing site.

- Manufacture of the Product

The manufacturing process involves the following conventional operations using standard equipment: mixing, high shear wet granulation, delumping, drying, sieving, blending, compression, coating and packaging. A manufacturing overage is used for all coating ingredients to guarantee an optimal film coat. Appropriate in-process controls are established in order to ensure that the specified chemical and physical properties of the tablets are achieved consistently.
Satisfactory validation data have been provided for 3 batches manufactured at the proposed commercial site and show that the manufacturing process is robust and well controlled.

- Product Specification

The product specification includes tests controlled by validated methods for appearance, colour, markings, uniformity of mass (PhEur), identity (HPLC and IR), assay, degradation products, dissolution (PhEur) and microbial purity (PhEur).
Batch analysis data provided for 2 partial full scales and 1 full-scale batch manufactured at the commercial manufacturing site meet the specification at the time of release and indicate consistent and reproducible manufacture.

- Stability of the Product

Stability data have been provided for 2 partial full scales and 1 full-scale batch manufactured at the commercial manufacturing site. 1-year and 6-month data are available for these batches under respectively long term (25ºC/60% RH - packaging intended for commercialisation) and accelerated conditions (40°C/75% RH - intended packaging). A photostability study has been performed. It showed that the product is not light sensitive.
The data provided support the proposed shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Invirase 500 mg film-coated tablet has been developed in order to support patient adherence to treatment by reducing daily pill burden. No change has been made to saquinavir mesylate active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process was developed and optimised to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the products are stable for the proposed shelf life.

1.3 Non-clinical aspects

This application does not concern any change in dosage or indication for Invirase.

No Module 4 has been provided with the present application since no nonclinical data have been generated in the context of the development of Invirase FCT. However, the MAH has submitted a short nonclinical overview, showing that most of the nonclinical data were already submitted with the original application while additional studies in monkeys (12 – month toxicity), rats and mice (carcinogenicity studies) were submitted between 1996 and 1998. The safe use of Invirase is based not only on the available nonclinical studies, but also on the broad clinical experience.

1.4 Clinical aspects

Introduction

The clinical development program for the Invirase FCT was based on the premise that, provided bioequivalence is demonstrated, a new preparation of solid dose forms can be expected to provide essentially similar efficacy and safety to the reference medication. Therefore, the development of the 500 mg Invirase FCT was based on three clinical pharmacology studies, i.e. one pivotal bioequivalence study as well as two supporting bioavailability studies:

- to investigate the relative bioavailability of the 500 mg Invirase FCT formulation compared to the existing 200 mg Invirase HC market formulation in combination with ritonavir 100 mg b.i.d. (Study BP17058)
- to demonstrate bioequivalence between these two formulations in combination with ritonavir 100 mg b.i.d. (Study BP17059)

to investigate saquinavir exposures following use of Invirase FCT and Invirase HC in the absence of ritonavir, to collect some information on pure product performance (Study BP17653 conducted at the request of the FDA).

Pharmacokinetics

1. Relative Bioavailability Pilot Study BP17058

This was an single-centre, open-label, randomised, two-sequence, four-period, two-treatment, replicated, crossover study comparing the bioavailability of the 500 mg saquinavir tablet (Invirase FCT) relative to the 200 mg saquinavir capsule (Invirase HC). Both saquinavir formulations were administered at a single dose of 1000 mg combined with ritonavir 100 mg under fed conditions (which is the presently approved single dose). Twenty healthy male volunteers aged 19 to 56 years were enrolled and were to receive ritonavir for 24 days (100 mg p.o., b.i.d.) and a single dose of saquinavir on days 14, 17, 20, and 23 as either Invirase HC (5 x 200 mg capsules) or Invirase FCT (2 x 500 mg tablets). The reference treatment (A) was Invirase HC + ritonavir and the test treatment (B) was Invirase FCT + ritonavir. Subjects were randomly assigned to the two treatment sequences ABAB and BABA. Blood samples for pharmacokinetic analysis were collected over 24 hours. Plasma concentrations of saquinavir were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with a quantification limit of 0.2 ng/mL. Primary pharmacokinetic parameters were $AUC_{0-\infty}$ and C_{max}. Of

the 20 subjects enrolled, 4 subjects withdrew from the study prematurely of whom two provided no saquinavir pharmacokinetic data.

Table 1 **Study BP17058: Estimated Mean Exposures and Mean Exposure Ratios (90% CI) for Saquinavir**

Exposure Parameter	Treatment	Estimated Mean Exposure[a]	Estimated Mean Exposure Ratio (90% CI) INV FCT/ritonavir vs INV HC/ritonavir
$AUC_{0-\infty}$ (h*ng/mL)	Invirase HC/ritonavir	21442	
	Invirase FCT/ritonavir	22485	1.05 (0.94, 1.18)
C_{max} (ng/mL)	Invirase HC/ritonavir	2930	
	Invirase FCT/ritonavir	3298	1.13 (1.00, 1.26)

a: exponentiated least squares means of ln-transformed exposure parameters
N=16 subjects

Mean saquinavir exposure in terms of both $AUC_{0-\infty}$ and C_{max} following administration of Invirase FCT/ritonavir was similar to that following administration of Invirase HC/ritonavir. In the case of C_{max} Invirase FCT/ritonavir showed a tendency for higher values than Invirase HC/ritonavir.

This was a pilot study, which followed the generally accepted criteria for bioavailability studies. The fact that for C_{max} the standard upper confidence interval of 1.25 has been slightly exceeded should not be overestimated since in the pivotal study BP17359 in a much greater number of subjects (see below) the bioequivalence criteria (90 % C.I. 0.80; 1.25) were fulfilled even for C_{max}.

2. Bioequivalence Study BP17359

This study was designed to establish bioequivalence of the Invirase FCT 500 mg to the Invirase HC 200 mg at a single dose of 1000 mg of saquinavir. Both formulations were administered under fed conditions and were combined with ritonavir 100 mg capsules. This was a two-center, open-label, randomised, two-treatment, two-sequence, four-period, replicated crossover study conducted in two centers. A total of 100 healthy (93 males and 7 females) volunteers aged 19 to 65 years were enrolled and were to receive ritonavir for 24 days (100 mg p.o., b.i.d.) and a single dose of saquinavir on days 14, 17, 20, and 23 as either Invirase HC (5 x 200 mg capsules) or Invirase FCT (2 x 500 mg tablets). The reference treatment (A) was Invirase HC + ritonavir and the test treatment (B) was Invirase FCT + ritonavir. Subjects were randomly assigned to the two treatment sequences ABAB and BABA, balancing the allocation with respect to site and gender. Blood samples for pharmacokinetic analysis were collected over 24 hours. Plasma concentrations of saquinavir were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with a quantification limit of 1 ng/mL. Primary pharmacokinetic parameters were $AUC_{0-\infty}$ and C_{max}. Of the 100 subjects enrolled, 6 subjects (all males) withdrew from the study prematurely and did not provide any saquinavir pharmacokinetic data.

Table 2 Study BP17359: Primary Pharmacokinetic Parameters of Saquinavir

Parameter		A: Invirase HC/ritonavir	B: Invirase FCT/ritonavir
Number of observations		188	188
$AUC_{0-\infty}$ (h*ng/mL)	Arithmetic Mean (CV%)	27805 (51%)	29734 (45%)
	Geometric Mean (CV%)	24430 (56%)	26826 (49%)
C_{max} (ng/mL)	Arithmetic Mean (CV%)	3322 (39%)	3911 (36%)
	Geometric Mean (CV%)	3064 (43%)	3644 (41%)

Table 3 Study BP17359: Primary Pharmacokinetic Parameters of Saquinavir by Gender

Parameter	A: Invirase HC/ritonavir		B: Invirase FCT/ritonavir	
	Male	Female	Male	Female
Number of observations	174	14	174	14
$AUC_{0-\infty}$ (h*ng/mL)	26384 (49%)	45459 (35%)	28407 (43%)	46224 (35%)
	23343 (54%)	43014 (36%)	25786 (48%)	43852 (34%)
C_{max} (ng/mL)	3267 (40%)	4005 (28%)	3808 (36%)	5201 (22%)
	3008 (44%)	3858 (30%)	3548 (40%)	5074 (24%)

Arithmetic means (arithmetic CV%) followed by geometric means (geometric CV%) are reported for $AUC_{0-\infty}$ and C_{max},

Bioequivalence of Invirase FCT and Invirase HC in combination with ritonavir was assessed based on the 90% confidence intervals for the mean exposure ratio derived from an ANOVA applied to the ln-transformed primary pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} using the standard acceptance criteria for bioequivalence (Table 4).

Table 4 Study BP17359: Estimated Mean Exposures and Mean Exposure Ratios (90% CI) for Saquinavir

Exposure Parameter	Treatment	Estimated Mean Exposure[a]	Estimated Mean Exposure Ratio Invirase FCT/r vs Invirase HC/r		
			Estimated Mean Exposure (%)	90% CI (%)	Conclusion
$AUC_{0-\infty}$	Invirase HC/ ritonavir	28420	100.00	Reference	
(h*ng/mL)	Invirase FCT/ ritonavir	31223	109.86	[104.41,115.59]	Equivalence
C_{max}	Invirase HC/ ritonavir	3295	100.00	Reference	
(ng/mL)	Invirase FCT/ ritonavir	3924	119.07	[113.67,124.72]	Equivalence
Equivalence Region (%):				[80.00, 125.00]	

a: exponentiated least squares means of ln-transformed exposure parameters
N = (7 Females + 87 Males) * 4 = 376 PK profiles

Bioequivalence of Invirase FCT/ritonavir and Invirase HC/ritonavir with respect to saquinavir was demonstrated.
Administration of Invirase FCT/ritonavir resulted in increased exposure to saquinavir compared to Invirase HC/ritonavir, both in terms of $AUC_{0-\infty}$ and C_{max}.

An investigation of the gender effect revealed that saquinavir exposures (AUC and C_{max}) after use of either Invirase FCT/r or Invirase HC/r were higher for female subjects (+56% for $AUC_{0-\infty}$ and +26% for C_{max}) than for male subjects (Table 5).

Table 5 Study BP17359: Estimated Mean Exposures and Mean Exposure Ratios for Saquinavir in Females versus Males

Exposure Parameter	Gender	Estimated Mean Exposure[a]	Estimated Mean Exposure Ratio (95 % CI) Females vs Males
$AUC_{0-\infty}$ (h*ng/mL)	Females	37203	1.56 (1.16, 2.10)
	Males	23852	
C_{max} (ng/mL)	Females	4044	1.26 (0.99, 1.62)
	Males	3198	

a: exponentiated least squares means of ln-transformed exposure parameters
N = (7 Females + 84 Males) * 4 PK Profiles

This pivotal study has demonstrated the bioequivalence between Invirase 200 mg HC and Invirase 500 mg FCT both on AUC (infinity) and on Cmax, although the saquinavir exposure after the FCT was a

little higher than after the HC, but still within the accepted range for bioequivalence (0.80 – 1.25). The study was adequately performed. The four-period crossover design obviously has been chosen in order to fulfil FDA requirements. It is appreciated that the MAH has not tried to widen the acceptance criteria for Cmax, but has chosen a number of almost 100 evaluable study subjects. In this respect the MAH has followed the advice, which has been given both by FDA and by the rapporteur in a pre-submission meeting. Under the conditions of the present experiment the Invirase FCT fulfils the accepted criteria of bioequivalence to the approved Invirase HC. This is especially remarkable when the known high variability in saquinavir exposure is taken into consideration.
The observed gender difference (higher saquinavir exposure in females than in males) is adequately reflected in the SmPC.

3. Relative Bioavailability Study BP17653

Study BP17653 was an open-label, randomised, two-sequence, four-period, two-treatment, replicated, crossover study assessing bioavailability of the Invirase FCT 500 mg relative to the Invirase HC 200 mg. Both saquinavir formulations were administered at a single dose of 1000 mg under fed conditions. Twenty healthy volunteers (10 male and 10 female subjects) aged 20 to 64 years were enrolled and received a single dose of 1000 mg saquinavir as either Invirase HC (5 x 200 mg capsules), treatment A, or Invirase FCT (2 x 500 mg tablets), treatment B, on four occasions two days apart. Subjects were randomly assigned to the two treatment sequences ABAB and BABA, balancing the allocation with respect to gender. Blood samples for pharmacokinetic analysis were collected over 24 hours. Plasma concentrations of saquinavir were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with a quantification limit of 0.2 ng/mL. Primary pharmacokinetic parameters were $AUC_{0-\infty}$ and C_{max}.

The bioavailability of Invirase FCT relative to Invirase HC was investigated by use of ANOVA methods applied to the ln-transformed primary pharmacokinetic parameters and therefrom derived estimates and 90% confidence intervals for the mean exposure ratio (Table 6).

Table 6 Study BP17653: Estimated Mean Exposures and Mean Exposure Ratios (90% CI) for Saquinavir

Exposure Parameter	Gender	Treatment	Estimated Mean Exposure[a]	Estimated Mean Exposure Ratio (90% CI) INV FCT vs INV HC
$AUC_{0-\infty}$ (h*ng/mL)[b]	Females	Invirase HC	1086	
		Invirase FCT	1485	1.37 (1.17, 1.59)
	Males	Invirase HC	1039	
		Invirase FCT	1028	0.99 (0.85, 1.15)
C_{max} (ng/mL)	Females	Invirase HC	306	
		Invirase FCT	395	1.29 (1.03, 1.62)
	Males	Invirase HC	265	
		Invirase FCT	278	1.05 (0.84, 1.31)
	All	Invirase HC	285	
		Invirase FCT	332	1.16 (0.99, 1.37)

a: exponentiated least squares means of ln-transformed exposure parameters
b: overall estimation (i.e. for females and males together) of mean exposures and exposure ratios for the two treatments not provided for AUC due to the finding of a gender-by-treatment interaction
N = (10 Females + 10 Males) *4 = 80 PK profiles

There is evidence for a difference in the relative performance of the two formulations between male and female healthy volunteers (gender-by-treatment interaction for $AUC_{0-\infty}$). With respect to $AUC_{0-\infty}$, higher exposures were observed in females compared to males following Invirase FCT but virtually no difference was found between the sexes following Invirase HC. Given the presence of this gender-by-treatment interaction for $AUC_{0-\infty}$, a common, gender independent estimate (i.e. for males and females together) of the treatment ratio for $AUC_{0-\infty}$ was not calculated.

With respect to C_{max} a higher increase was observed in females than in males when administered the tablet formulation compared to the capsule. There was, however, no indication of a gender-by-treatment

interaction and the results did not provide clear evidence for a difference between treatments or gender with respect to C_{max}.

In summary, comparable pharmacokinetic properties were observed for Invirase FCT and Invirase HC with the possible exception of a higher $AUC_{0-\infty}$ following Invirase FCT compared with HC in female subjects.

Formally this study has not fulfilled the accepted criteria for bioequivalence since the upper 90 % C.I. is above 1.25. Nevertheless this study is the least relevant of the three submitted bioavailability/bioequivalence studies with respect to the clinical use of this drug. The very low saquinavir exposure in subjects that did not receive ritonavir is demonstrating once again that in clinical practice saquinavir no longer should be given without ritonavir.

Comments

1. *The quantification limit for saquinavir in the pivotal study BP17359 was 1 ng/ml while in the smaller studies BP17058 and BP17653 it was five times lower (i.e. 0.2 ng/ml).* However, the change of the LOQ from 0.200 ng/ml to 1.00 ng/ml had no impact on the PK parameters C_{max} and $AUC_{0-\infty}$ and therefore on the results of the pivotal bioequivalence results. Because the pilot study (BP17058) and the pivotal study (BP17359) were performed in sequential order, the adjustment of the LOQ for saquinavir in study BP17359 was based on the results from study BP17058.

In the pilot study (BP17058), where saquinavir/ritonavir was administered, the quantification limit for saquinavir was chosen to be 0.200 ng/ml (calibration range 0.200-100 ng/ml) to ensure that low saquinavir plasma concentrations could be measured. Based on the saquinavir-concentration-time profile obtained in the pilot study it became clear that saquinavir plasma concentrations were very high, and a LOQ of 1.00 ng/ml would be sufficient to adequately characterize the plasma concentration profile. In addition, the calibration range was increased up to 7500 ng/ml in order to minimize the dilution steps required during sample preparation.

In study BP17653, saquinavir was administered without ritonavir, and therefore much lower saquinavir plasma concentrations were anticipated based on prior experience with saquinavir monotherapy. In order to obtain measurable concentrations over the entire concentration time profile, the LOQ for saquinavir was retained at 0.200 ng/ml for this monotherapy study.

2. *There was no indication as to the terms included in the ANOVA model, in particular whether these included sequence and period, as recommended in the Note for guidance*. This was however clarified.

3. *It was requested that definite evidence be provided to support the use of intervals of three days between saquinavir doses*. Based on the half-life considerations and the negligible residual concentrations at pre-dose, it can be concluded that the use of intervals of three days between saquinavir doses was appropriate for the purpose of the study.

4. *The MAH was requested to justify why no bioequivalence trial comparing Invirase FCT and Fortovase (each boosted) has been performed. This request for a clarification is based on the view that in clinical practice also Invirase FCT and Fortovase may be considered "interchangeable", and will be, foreseeable, interchanged in the future. In addition, the MAH was requested to clarify whether it is planning to investigate bioequivalence of saquinavir of both products.*

The rationale for including Invirase Hard Capsule (HC) as the comparator is that the active ingredient in the Invirase Film-coated Tablet (FCT) is the same as in Invirase HC, i.e. saquinavir mesylate. Furthermore, Invirase HC leads to comparable saquinavir exposure as Fortovase Soft Capsule (SC) when boosted with ritonavir (saquinavir/ritonavir 1000/100 mg bid). This allows switching between Fortovase/ritonavir and Invirase/ritonavir. Additionally, Invirase Film-coated Tablets and Hard Capsules have advantages over the Fortovase formulation as they are easier to swallow due to their smaller size, they can also be stored at room temperature (Fortovase needs refrigeration). Invirase HC has become the preferred saquinavir formulation in combination with ritonavir. Based on the interchangeability between

Fortovase/ritonavir and Invirase/ritonavir, the MAH does not intend to perform another bioequivalence study using as comparator Fortovase Soft Capsules. Furthermore, the choice of the comparator for the bioequivalence study has been discussed and Invirase 200 mg HC has been approved as comparator at a pre-submission meeting between the Rapporteur and Roche on the saquinavir 500 mg Film-coated Tablet.

5. *Boosted saquinavir is recommended with food intake, but there is no information in the SPC to justify this recommendation. Hence, the MAH was requested to provide information on the effect of food on ritonavir-boosted saquinavir. If this information is not available this should be investigated, and in the meantime a sentence should be added to section 5.2 of the SPC that currently there is no information available on the effect of food on ritonavir-boosted saquinavir.*

The justification for this recommendation is as follows. The pivotal studies for the ritonavir boosted saquinavir regimen as well as the PK bridging study (from Fortovase/ritonavir to Invirase/ritonavir) were performed with food. Therefore, all the data (efficacy, safety, and pharmacokinetics) collected with saquinavir/ritonavir 1000/100 mg bid are based on administration with food. This leads to the recommendation to give boosted saquinavir with food which is reflected in section 4.2 of the currently approved SPCs of Fortovase Soft Capsules (SC) and Invirase Hard Capsules (HC) as well as in the proposal for the SPC of Invirase Film-coated Tablets (FCT). The recommendation to give ritonavir boosted saquinavir with food dates back to the Type II Variation for the new dosing regimen Invirase/ritonavir or Fortovase/ritonavir 1000 /100 mg bid.

The MAH proposes to address this question by adding in section 5.2 of the SPC a sentence saying that no food effect data are available for Invirase in combination with ritonavir.

The current approved labels of Fortovase SC and Invirase HC as well as the proposed label for Invirase FCT are recommending clearly that the drug combination needs to be taken with food. The MAH has no intent to alter this recommendation.

However, on request from CHMP, the MAH commits to investigate the effect of food on boosted saquinavir to clarify if there is a scientific rationale for the current recommendation that the combination should be taken within 2 hours following a meal. The reason for this is that if the food effect on boosted saquinavir is small and if, in the individual patient, intake in the fasting state is tolerable, this could be a useful option.

Pharmacodynamics

Not applicable

Clinical efficacy

Not applicable

Clinical safety

The safety profile of the Invirase FCT formulation has been determined in the three pharmacokinetic studies conducted in healthy volunteers.

The vast majority of healthy volunteers in these three trials received all doses of study treatment and completed the study according to the protocol. There were no withdrawals from study BP17653. Four subjects were withdrawn prematurely from study BP17058, one due to an adverse event prior to the first scheduled dose of saquinavir, a second withdrew consent due to personal reasons and the remaining two due to protocol violations. Six subjects were withdrawn from study BP17359. Four subjects were withdrawn due to adverse events prior to the first scheduled day of saquinavir dosing, one was withdrawn due to an adverse event after receiving the first dose of saquinavir and the sixth subject withdrew consent due to personal commitments on Day 2 of dosing with ritonavir.

In the healthy volunteer studies no concomitant medication was permitted, with the exception of medications to treat adverse events.

Adverse Events

As the bioavailability/bioequivalence studies BP17058 and BP17359 were of a similar design and involved similar subject populations, the safety data from these trials have been pooled in order to better reflect the frequency of adverse events reported during treatment with the Invirase FCT formulation. These data are presented separately from the data derived from the unboosted saquinavir bioavailability study BP17653.

Overall, the Invirase FCT and Invirase HC formulations were equally well tolerated by healthy volunteers and the types of adverse event seen were similar to those following the Fortovase SC formulation in the patient studies. There were no unexpected adverse events in any of the healthy volunteers or patient studies. Overall, the most common adverse events were gastrointestinal disorders, a finding that is consistent with the current product label.

1. Ritonavir Boosted Studies BP17058/BP17359 (Pooled Dataset)

A total of 72 subjects (60.0%) reported 144 adverse events during the ritonavir 100 mg b.i.d. run-in period compared with 25 subjects (22.1%) reporting 35 adverse events during the Invirase HC/ritonavir treatment periods and 33 subjects (29.7%) reporting 40 adverse events during the Invirase FCT/ritonavir periods. Headache was the most frequently reported adverse event throughout the study [11 subjects (9.7%) versus 15 subjects (13.5%) in the HC/ritonavir and FCT/ritonavir periods, respectively]. This compares with 30 subjects (25.0%) reporting headache during the ritonavir alone run-in period.
'Gastrointestinal disorders' was the most frequently reported body system throughout the study. A total of 31 subjects (25.8%) reported at least one incidence of a gastrointestinal disorder during the ritonavir run-in period compared with 13 subjects (11.5%) during the Invirase HC/ritonavir periods and 18 subjects (16.2%) during the Invirase FCT/ritonavir periods. Diarrhoea was the gastrointestinal disorder reported with the highest frequency. This event was recorded by 15 subjects (12.5%) during the ritonavir run-in period, 6 subjects (5.3%) during the Invirase HC/ritonavir periods and 7 subjects (6.3%) during the Invirase FCT/ritonavir treatment periods. Nausea, reported by 3 subjects (2.7%), loose stools reported by 3 subjects (2.7%), watery stools reported by 3 subjects (2.7%) and abdominal pain reported by 4 subjects (3.6%) were the only other gastrointestinal disorders reported during the Invirase FCT/ritonavir treatment periods.

The temporal association between the occurrence of adverse events recorded during the study and the administration of saquinavir was further investigated by summarizing all adverse events, which occurred within 48 hours of administration of the scheduled dose (phase) of Invirase HC/ritonavir or Invirase FCT/ritonavir according to the subjects' randomisation schedule. Headache was the only adverse event, which appeared to show any temporal relationship to Invirase administration. Of the subjects randomised to receive Invirase FCT in combination with ritonavir as the first phase of saquinavir dosing, 10 (18.0%) reported a headache within the 48 hours immediately following dosing. During the remaining 3 phases (Invirase HC/ritonavir, Invirase FCT/ritonavir, Invirase HC/ritonavir) for this randomised group, headache was reported only three times, always by patients who had previously reported the event. In the group of subjects randomised to receive Invirase HC in combination with ritonavir as the first phase of saquinavir dosing, no differences were identified in the occurrence of headache between this phase and the following three dose phases.

No deaths or serious adverse events were recorded in any of the healthy volunteer. Despite the significant gender effect with regard to exposure in the healthy volunteer studies, and the slightly higher occurrence of adverse events in female subjects than in male subjects in the unboosted study BP17653, the adverse event profiles of the 500 mg Invirase FCT or 200 mg Invirase HC did not differ markedly between male and female subjects.

2. Unboosted Bioavailability Study BP17653

In general, both the Invirase FCT and Invirase HC treatments were well tolerated. A total of 17 subjects (85.0%) reported 38 adverse events following Invirase FCT treatment compared with 14 subjects (70.0%) reporting 25 adverse events following Invirase HC. (Venipuncture site bruise was the most frequently reported adverse event in each period [10 subjects (50.0%) versus 7 subjects (35.0%) in the FCT and HC periods, respectively].

A marginally higher incidence of gastrointestinal disorders was seen following Invirase FCT treatment compared with Invirase HC treatment. Abdominal pain (3 subjects versus 0 subjects), loose stools (2 subjects versus 1 subject) and nausea (2 subjects versus 1 subject) were all reported by a slightly greater number of subjects during the Invirase FCT treatment periods. In contrast, infrequent bowel movement was reported by 1 subject following Invirase HC treatment but was absent in the Invirase FCT treatment periods.

Comments

1. *Regardless of meeting the bioequivalence criteria, the MAH was asked to discuss the potential effects of higher saquinavir exposures on taking the new 500 mg film-coated tablet formulation."*

2. The submitted bioequivalence studies clearly indicate that there is a sex difference in saquinavir exposure for boosted saquinavir, with females showing higher exposure than men. The MAH has added a paragraph in section 5.2 Effect of gender, stating that "A clinically significant difference in safety profile and efficacy between men and women has not been reported with the approved dosage regimen". This statement should be supported by relevant efficacy and safety data, or the sentence should be changed to read: "It has not been investigated if the sex difference in exposure results in a clinically significant difference in safety profile or efficacy between men and women has not been investigated

3. The MAH was invited to further substantiate the observed gender differences in the light of current knowledge (at least by a critical overview of the published literature), especially regarding the relationship between plasma levels and safety, and the applicant should give clear recommendation in terms of therapeutic management of male and female patients.

4. The MAH was requested to submit a meta-analysis on gender effect concerning all data available as regards to efficacy and safety of boosted saquinavir, preferentially data derived from larger (not less than 200 patients) randomised controlled clinical trials.

Questions 1,2, 3 and 4 are considered by the MAH to all relate to the same general issue. As a consequence, responses to these questions have been combined to provide a single consolidated response as the issues raised in each are linked to the same observation.

Data from two large studies of the Fortovase-ritonavir combination regimen were explored to investigate whether there is any evidence for a concentration driven deterioration in safety profile. The consistency of the observations across the studies evaluated is reassuring. The results suggest that there is no significant relationship between saquinavir drug levels and the nature or severity of the majority of adverse events experienced by patients treated with saquinavir/ritonavir. There is a possible slight association with increasing severity of gastrointestinal events reported and the time of onset of an event in an affected individual. However, gastrointestinal symptoms are usually considered to be "nuisance" effects and were not medically significant in most cases. Importantly there appeared to be no relationship between saquinavir concentrations and serious adverse events in any study. The data support the excellent safety profile of saquinavir and provide a measure of reassurance that the potential for a modest increase in overall exposures following introduction of the film coated tablet is unlikely to result in a worsening safety profile of the product in everyday use in clinical practice.
A gender effect, noted in the bioequivalence study, prompted an evaluation of gender specific effects. A small increase in adverse event reporting rates was noted in women enrolled in these studies. Higher adverse event frequencies among women have been reported in other trials in HIV infected patients.

In a study of ritonavir use, women reported more frequent and severe side effects than men, particularly gastrointestinal and neurological side effects. The frequency of these events corresponded to higher plasma concentrations of ritonavir in women than men given the same dose. Other investigators have reported that women have a higher incidence of neuropathy and safety driven regimen changes higher rates of gastrointestinal disturbance and higher rates of allergic reactions, neurologic side effects, gastrointestinal problems, and symptoms of nephrolithiasis than men. Women also suffer from a greater number of adverse events, such as neuropathy, while taking nucleoside reverse transcriptase inhibitors (NRTIs), than men possibly owing to increased levels of the active anabolites because of gender related differences in phosphorylation rate. It is therefore unsurprising that a higher proportion of women enrolled in MaxCmin 1 and MaxCmin 2 reported adverse events, particularly gastrointestinal events, than men. However, neither the frequency nor the severity of events reported appeared to correlate significantly with observed saquinavir plasma concentrations, so these effects may be a result of gender bias in reporting tendency rather than a result of concentration related toxicity.

Fletcher *et al*. recently reported the efficacy and safety data from ACTG 359. Saquinavir was common in all study arms, and the study investigated relationships among characteristics of patients, saquinavir area under the curve (AUC), trough concentrations (C_{min}) and virologic response. Females had higher AUC and C_{min} values than did males. Higher saquinavir AUC and C_{min} values were associated with a greater likelihood of human immunodeficiency virus (HIV) RNA levels ≤ 500 copies/mL (p=0.008). Males had a lower probability of having HIV RNA levels ≤ 500 copies/mL at week 16 than did females (28% versus. 42%; adjusted odds ratio, 0.43). Gender specific safety data have not been reported from ACTG 359 at present; however the safety profile observed in this study is good. These data support the conclusion that saquinavir is well tolerated by both women and men. A breakdown of the efficacy data from MaxCmin 1 and MaxCmin 2 support the conclusion that the combination is efficacious in both men and women.

In summary, the MAH believes that the introduction of the Invirase 500 mg film coated tablet into clinical practice has a positive benefit risk profile as it significantly decreases the pill burden while retaining the efficacy and safety profile of the currently approved dose form. There are no significant differences between men and women that justify differential treatment based on gender. Efficacy is assured in both men and women. Although women may report adverse experience more frequently than men, the differences observed are medically unimportant and there is no clear relationship between adverse event experience and blood plasma saquinavir concentrations in either men or in women.

It is concluded that the proposed text in Section 5.2 of the SPC, which describes the gender specific differences in concentrations and concludes "Limited data from controlled clinical studies with the approved dosage regimen do not indicate a major difference in the efficacy and safety profile between men and women." is supported by the available evidence.

The MAH also gives a commitment to amend the SPCs of Invirase 200 mg hard capsules and Fortovase 200 mg soft capsules with respect to gender effect as Type II variations.

1.5 Product literature

The SPC and PL have been adapted according to the outcome of the variation procedure EMEA/H/C/113/II/44.

1.5.1 Except for some minor modification, the SPC changes (taking into account QRD comments) as proposed by the MAH are acceptable.

- The MAH has revised the SPC section on the "Effect of Gender" as follows:

  "Effect of gender following treatment with Invirase/ritonavir: ~~*No effect of gender was observed on the pharmacokinetics of Invirase 200 mg hard capsule administered as a 600 mg single dose in 71 healthy volunteers.*~~ *A gender difference was observed with females showing higher saquinavir exposure than males (AUC 56%, C_{max} 26%) in the bioequivalence study comparing*

Invirase 500 mg film coated tablets with Invirase 200 mg hard capsules both in combination with ritonavir. There was no evidence that age and body-weight explained the gender difference in this study. A clinically significant difference in safety profile and efficacy between men and women has not been reported with the approved dosage regimen~~. Treatment with saquinavir/ritonavir 1000/100 mg bid in male and female patients is found to be safe and effective."~~

The justification for this proposed new wording is provided under the response to comments 1, 2, 3 and 4 in section *" Clinical safety"* of this assessment report.

The revised SPC proposal is generally endorsed but data from controlled clinical studies are limited with respect to a possible difference in the safety/efficacy profile between men and women. However, "experience" with the approved dosage regimen of boosted saquinavir may be quite extensive meanwhile. Therefore, the respective paragraph should read as follows:

"Effect of gender following treatment with Invirase/ritonavir: A gender difference was observed with females showing higher saquinavir exposure than males (AUC on average 56% higher and C_{max} on average 26% higher) in the bioequivalence study comparing Invirase 500 mg film coated tablets with Invirase 200 mg hard capsules both in combination with ritonavir. There was no evidence that age and body-weight explained the gender difference in this study. ~~A clinically significant~~ Based on limited experience, no major ~~difference in safety profile and efficacy between men and women has not been reported with the approved dosage regimen.~~ Limited data from controlled clinical studies with the approved dosage regimen do not indicate a major difference in the efficacy and safety profile between men and women."

- On the one hand it is stated that the medicinal product should be taken with food, on the other hand it says that there is no data available on the effect of food on boosted saquinavir. Without the respective background information, this might appear misleading to the reader. Therefore CHMP proposes to reword the text in section 5.2 of SPC as follows:

  "In HIV-infected patients, Invirase or Fortovase in combination with ritonavir at doses of 1000/100 mg bid provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with Fortovase 1200 mg tid (see Table 3). The pharmacokinetics of saquinavir are stable during long-term treatment. ~~No food effect data are available for Invirase in combination with ritonavir.~~ Studies with saquinavir in combination with ritonavir have been performed with food only. No data are available for the intake of ritonavir boosted saquinavir in the fasting state. "

- The CHMP also requests that information included in the SPC, *e.g*. in section 4.4, 4.5, 4.8, 5.1 and 5.2, be revised to better comply with recommendations in the "Note for Guidance on the clinical development of medicinal products for the treatment of HIV infection". At present the text mirrors the cumulative growth of experience of saquinavir when it should rather be focusing on the currently approved regimen of boosted saquinavir.

1.5.2 All PL changes as proposed by the MAH are acceptable.

1.5.3 All labelling changes as proposed by the MAH are acceptable.

1.5.4 Important safety data received on 03 February 2005

In a clinical pharmacology study in healthy volunteers, 11/28 (39.3%) subjects exposed to rifampicin 600 mg daily taken together with ritonavir 100 mg and saquinavir 1000 mg given twice daily (ritonavir boosted saquinavir) developed significant hepatocellular toxicity. One subject was admitted to hospital with mild liver failure. Dosing was immediately interrupted and the study discontinued immediately. Liver function tests in all affected subjects are returning to normal following drugs discontinuation. As a result of these findings, Roche advises that Rifampicin SHOULD NOT be used in patients also receiving saquinavir/ritonavir as part of combination antiretroviral therapy (ART). Roche has distributed a Dear Health Care Provider Letter in which information on these findings is given. The MAH has to submit Type II variations for all saquinavir containing products with respect to the following SPC changes as soon as possible:

- In section 4.3 rifampicine has to be included to the list of substances contraindicated for use in patients receiving saquinavir/ritonavir as part of combination antiretroviral therapy
- The sections 4.4, 4.5 and 4.8 have to be adapted in order to provide the relevant new information on hepatotoxicty when rifampicin and saquinavir/ritonavir age given concomitantly.

1.6 Overall conclusions, benefit/risk 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

Not applicable

Clinical Pharmacology

The MAH has submitted three bioavailability / bioequivalence studies with Invirase FCT versus the authorised reference product Invirase HC. Bioequivalence has adequately been demonstrated in the pivotal study BP17539. Similar bioavailability (although not formal bioequivalence) has been demonstrated in the pilot study BP17538. No bioequivalence has been demonstrated in study BP17653 in which saquinavir was given without ritonavir; this posology is no longer recommended. In the opinion of the CHMP no further pharmacokinetic studies are necessary with respect to the authorisation of Invirase 500 mg FCT.

No clinical safety studies using the 500 mg Invirase FCT formulation in a patient population were performed during the development program and the safety data derived from the phase I studies in healthy volunteers is of limited value due to the single dose nature of these studies. Based on the results and the gender effect noted in the healthy volunteer studies whereby females had higher saquinavir exposures than males following administration of either Invirase FCT or Invirase HC in combination with ritonavir, additional supplemental safety analyses have been provided to assess the possibility that tolerability may be affected given a modest increase in saquinavir exposures. Steady state plasma concentrations of saquinavir following treatment with 1000/100 mg b.i.d. Invirase FCT/ritonavir were predicted from the observed saquinavir exposure in a pharmacokinetic study in patients administered Invirase HC/ritonavir and Fortovase SC/ritonavir. The predicted saquinavir exposure following administration of 1000/100 mg b.i.d. Invirase FCT/ritonavir was shown to lie in the range of the observed exposure data in patients receiving Invirase HC/ritonavir and Fortovase SC/ritonavir.

Overall, the data suggest that the modest increase in exposures seen following administration of the film coated tablet to healthy volunteers is unlikely to result in a worsening safety profile of the product in patients.

The new 500 mg Invirase FCT formulation is not yet licensed in any region. Therefore there is currently no post-marketing data for this product.

The safety data, which were gathered in the three pharmacokinetic studies, should not be overestimated since one cannot compare the administration of single doses of Invirase in healthy volunteers with the administration of therapeutic doses of Invirase in HIV infected patients. One can just conclude that the safety data in healthy volunteers have not shown any new signal, which would change the known benefit/risk ratio of saquinavir.

Benefit/risk assessment

The benefit/risk ratio of Invirase 500 mg FCT is not different from that of the authorised Invirase 200 mg HC. Since the new 500 mg film-coated tablet enables the reduction of the "pill burden" to the patient from 10 to 4 saquinavir containing units per day, compliance might be improved, and this is an advantage to the therapy. Hence, it is deemed that the benefit / risk ratio of Invirase 500 mg film-coated tablets is positive.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Invirase 500 mg film-coated tablets in the following indication "Invirase is indicated for the treatment of HIV-1 infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products" was favourable and therefore recommended the granting of the marketing authorisation for this new strength.