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Assessment Report for Invirase

International Non-proprietary Name: **saquinavir**

Procedure number: **EMEA/H/C/000113/A-20/0088**

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

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1. Background information on the procedure

Invirase (saquinavir [SQV]) is an inhibitor of the HIV viral protease preventing the creation of mature infectious virus particles. Invirase is approved in several countries including the United States, Switzerland, Canada and Australia, and was the first protease inhibitor (PI) approved for the treatment of HIV-infected adult patients in the European Union via the Centralised procedure in 1996. Invirase is recommended to be used only in combination with ritonavir and other antiretroviral medicinal products. The recommended dose is 1000 mg twice daily with ritonavir 100 mg twice daily. Invirase is available in 200 mg capsules and 500 mg tablets.

A publication in *The Lancet* (Lancet 2005; 365: 682-686) reported cases of QT prolongation in patients receiving PIs and showed dose dependent blockage of hERG channels *in vitro* for saquinavir, lopinavir, nelfinavir and ritonavir. On request of the Food and Drug Administration (FDA) the Marketing Authorisation Holder (MAH) of Invirase conducted two studies (supra-therapeutic dose finding study [NP 21562] and thorough QTc study [NP 21249]) to investigate the effect of saquinavir boosted with ritonavir (SQV/r) on the QT interval in healthy volunteers. These studies were assessed by the CHMP in the scope of a type II variation in June 2010 (EMEA/H/C/113/II/085). The thorough QTc-study (NP21249) showed a dose dependent, significant prolongation of the QT interval and PR interval with both therapeutic and supra-therapeutic dose regimens of saquinavir.

Based on the data available in the framework of the type II variation and on the magnitude of the QT prolongation observed, the CHMP at its June 2010 plenary meeting agreed to introduce amendments to the product information for Invirase. Namely, to contraindicate the use of Invirase in patients with high risk for arrhythmias and concomitant use with other medicinal products that may cause QT and/or PR prolongation. Warnings for its use in patients with moderate risk (based on increased exposure) together with recommendations for ECG monitoring were also included. Further amendments were made in the interaction and pharmacodynamic sections of the Summary of Product Characteristic (SmPC) and respective sections of the Package Leaflet (PL).

Furthermore, to minimise the identified risk, the CHMP agreed with the immediate dissemination of these findings to health care professionals through the distribution of a Direct Healthcare Professional Communication. The MAH also committed to further explore and submit potential electrophysiological investigations in non-clinical settings that may increase the understanding of the observed effects (including the PR-prolongation, QT-prolongation and the observed discrepancy between T_{max} and the effect on QT interval).

However, the magnitude of the QT and PR changes observed and the uncertainty whether the maximum effect was captured in the QTc study (NP 21249) remained of concern to the CHMP. The seriousness of the effect seen and any potential clinical impact on the safe and effective use of SQV/r in combination treatment of HIV-1 infected adult patients were also of concern, particularly considering that alternative products with a probably better safety profile are available.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 24 June 2010 to assess the above concerns and its impact on the risk benefit balance for Invirase, and to give its opinion as to whether measures are necessary to ensure the safe and effective use of Invirase, and specifically whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

An article published in *The Lancet* reported cases of QT prolongation in patients receiving PIs and showed dose dependent blockage of hERG channels *in vitro* for saquinavir, lopinavir, nelfinavir and ritonavir. The MAH of Invirase conducted two studies (NP 21562 and NP 21249) to investigate the effect of SQV/r on the QT interval in healthy volunteers.

Study NP 21562, was a multiple ascending dose (MAD) study conducted in healthy volunteers to determine an appropriate supra-therapeutic dose of SQV/rtv to be used in the thorough QT/QTc study (study NP21249). Study NP 21249 evaluated the effects of the therapeutic (1000/100 mg twice daily) and supra-therapeutic (1500/100 mg twice daily) doses of Invirase on the QT interval in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) in healthy volunteers (N=59).

Results of the thorough QT/QTc study in healthy volunteers demonstrated dose dependent QT and PR prolongation with the therapeutic dose of saquinavir 1000 mg boosted with ritonavir 100 mg bid on day 3 and has identified an average maximum prolongation of QT interval by 18.86 milliseconds (ms) at 12 hours post dose compared to a single dose of moxifloxacin 400 mg of 12.18 ms at 4 hrs post dose. There were no reports of QT prolongation >500 ms nor of Torsades de Points (TdP).

The QT prolongation seen in this study was greater than that seen with moxifloxacin control. Dedicated QT studies of other protease inhibitors have not shown such degree of prolongation. However cross-study comparisons should be interpreted with caution due to differences in study drugs, doses chosen, timing of ECG monitoring relative to maximal plasma concentrations, design, conduct and analysis. Given these findings, the CHMP in June 2010 during the assessment of the type II variation (EMEA/H/C/113/II/085), agreed on amendments to the Product information of Invirase to reflect that:

- Invirase is contraindicated in patients with congenital or documented acquired QT prolongation, electrolyte disturbances, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias, as well as concurrent therapy with other drugs that prolong the QT and/or PR interval;
- Patients initiating therapy with SQV/r should be warned of the potential arrhythmogenic risk and told to report any signs of cardiac arrhythmias (e.g., chest palpitations, syncope, presyncope) to their physician. SQV/r should be discontinued in case of significant arrhythmias, QT or PR prolongation;
- Consideration should be given for performing baseline and follow-up ECGs after initiation of treatment in patients with predisposing risk factors or in patients taking concomitant medication known to increase the exposure of saquinavir. An ECG and continuous monitoring should be performed if signs or symptoms suggesting cardiac arrhythmia occur.

This information was disseminated to the HIV treating physicians and cardiologists via a Dear Health Care Professional Communication.

Additionally the MAH committed to conduct *in* vitro and *in vivo studies to* elucidate the electrophysiological properties of SQV/r and to gain a better understanding of the delayed effect on QT prolongation relative to C_{max} observed in the clinical thorough QT study.

Notwithstanding the above measures agreed, the magnitude of the QT and PR changes observed and the uncertainty whether the maximum effect was captured in the QTc study remained of concern to the CHMP. The seriousness of the effect seen and any potential clinical impact on the safe and effective use of SQV/r in combination treatment of HIV-1 infected adult patients were also of concern, particularly considering the known safety profile of other available treatments.

Therefore a review of the benefit and risk of Invirase was started. The MAH was asked to specifically provide any preclinical data relevant to the assessment of the cardiovascular safety of Invirase, to discuss the clinical relevance of the results of the QT study in light of the clinical experience, the uncertainly whether the maximum effect has been observed and the potential cardiovascular risk of HIV patients. The MAH was also asked to discuss the current place of Invirase in the treatment of HIV infection considering the recent cardiovascular findings and the new contraindications and warnings introduced in the product information. A Risk Management Plan with proposals for further measures was also requested. The MAH responses are summarised and discussed hereafter.

2.1. Non-clinical aspects

Preclinical data available with saquinavir pertaining to cardiovascular safety with respect to the ECG was obtained from regulatory toxicology studies in dogs and marmosets with the exception of two early general pharmacology studies that used anesthetised cats. No treatment-related effects on the ECG intervals or morphology were seen in these studies.

The article published in *The Lancet* in 2005, showed in an *in vitro* electrophysiological assay using hERG channels expressed in HEK293 cells, that saquinavir had an IC_{50} of 15.3 μM for blockade of the hERG current. While for the other tested PIs the IC_{50}'s were 8.6 μM for lopinavir, 11.5 μM for nelfinavir, and 8.2 μM for ritonavir.

It was acknowledged by the MAH that in the toxicology studies the exposures of saquinavir were below the IC_{50} for hERG inhibition of 15.3 μM, with the exception of the ritonavir-boosted toxicology in dogs using highest doses of 2000mg/kg/day SQV and 250mg/kg/day RTV, respectively.

The MAH will conduct three additional preclinical studies as a post-approval commitment of the type II variation in June 2010. Two studies will evaluate the potential for SQV to affect cardiac ion channels, the other will look at the distribution of saquinavir in cardiac tissue relative to plasma concentration. The protocol of these studies have been reviewed and agreed with the CHMP in follow-up measures. The final results of these studies are expected during Q1 of 2011.

Conclusions
No effects on ECG intervals or morphology were observed in any of the toxicology and pharmacology studies available. It was noted that in most of the toxicology studies, the achieved exposures of SQV were below the IC50 of 15.3 μM for blockade of the hERG current identified in the Lancet 2005 publication. Therefore the relevance of the toxicology/pharmacology studies in this context is limited. The follow-up *in vitro* studies and the tissue distribution study are expected to increase the understanding of the mechanism of saquinavir effects on QT- and PR-interval. The final study results will be available during Q1 of 2011.

2.2. Clinical aspects

2.2.1. Clinical pharmacology

Overview of the pharmacokinetic studies: NP 21562 and NP21249

Study NP21562 was a 14-day, randomised, double-blind, multiple ascending dose (MAD) study conducted in healthy volunteers to determine an appropriate supra-therapeutic dose of SQV/rtv to be used in the thorough QT/QTc study (study NP21249). Dose escalation was based on thorough review of safety data (i.e. laboratory safety data, vital signs, ECGs), tolerability and pharmacokinetics parameters for saquinavir. After completion of the first dose cohort of SQV/rtv (1500/100 mg bid, n =

9; and 1000/100 mg bid, n = 3), the PK data suggested that further dose escalation could result in SQV exposure greater than the highest exposure observed in 4-week dog toxicokinetic studies (AUC_{0-24} = 168 µg.h/ml).

The maximum AUC_{inf} and AUC_{12h} in two subjects who received the 1500/100 mg SQV/r twice a day (bid) were 83.4 µg.h/ml and 80.2 µg.h/ml, respectively. On the assumption that the absorption of the next higher planned dose (2000/100 mg SQV/r bid) would be of the same rate as the absorption at the 1500/100 mg SQV/r bid dose, the predicted AUC_{inf} and AUC_{12h} were estimated to be 98.6 and 91.7 µg.h/ml, respectively. Hence, further dose escalation of SQV/r to 2000/100 mg bid mg could result in daily exposures exceeding the highest exposure tested in the dog toxicology studies (AUC= 84 µg.h/ml for a 12-hour dosing interval). Having met two pre-defined stopping criteria no further dose levels were investigated. This study also showed that maximum exposure was reached on Day 3.

Study NP21249 evaluated the effects of the therapeutic (1000/100 mg bid) and supra-therapeutic (1500/100 mg bid) doses of Invirase on the QT interval in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) in healthy volunteers (N=59).

On Day 3 of dosing, ECG measurements were done over a period of 20 hours. On Day 3 mean C_{max} values were approximately 3-fold and 4-fold higher with the therapeutic and supra-therapeutic doses, respectively, relative to the mean C_{max} observed at steady state with the therapeutic dose administered to HIV patients. On Day 3, the upper 1-sided 95% confidence interval of the maximum mean difference from pre-dose baseline-corrected QTcS (study specific heart rate corrected QT) compared to placebo was > 10 msec for the two ritonavir-boosted Invirase treatment groups (see table 1.). While the supra-therapeutic dose of Invirase/ritonavir appeared to have a greater effect on the QT interval than the therapeutic dose of Invirase/ritonavir, it is not sure if maximum effect for both doses has been observed. In the therapeutic and the supra-therapeutic arm 11% and 18% of subjects, respectively, had a QTcS between 450 and 480 msec. There were no QT prolongations > 500 msec and no Torsade de Pointes in the study.

Table 1. Maximum mean of ddQTcS† (msec) on day 3 for therapeutic dose of Invirase/ritonavir, supra-therapeutic dose of Invirase/ritonavir and active control moxifloxacin in healthy volunteers

Treatment	Post-Dose Time Point	Mean ddQTcS	Standard Error	Upper 95%-CI of ddQTcS
Invirase/ritonavir 1000/100 mg BID	12 hours	18.86	1.91	22.01
Invirase/ritonavir 1500/100 mg BID	20 hours	30.22	1.91	33.36
Moxifloxacin^	4 hours	12.18	1.93	15.36

† Derived change of pre-dose baseline corrected QTcS compared to placebo
^ 400 mg was administered only on Day 3
Note: QTcS in this study was QT/RR0.319 for males and QT/RR0.337 for females, which are similar to Fridericia's correction (QTcF=QT/RR0.333).

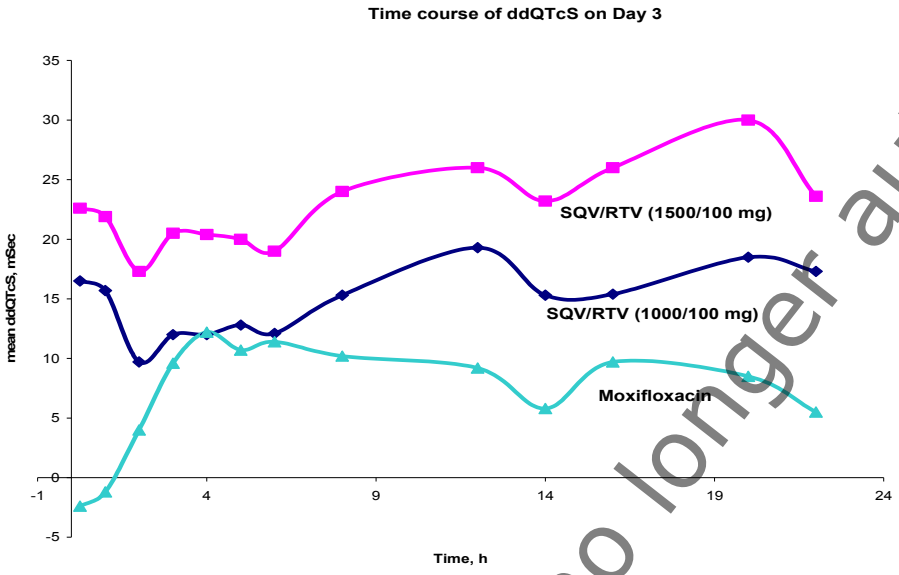
In this study PR interval prolongation of > 200 msec was also observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, on Day 3. PR prolongations of > 200 msec were seen in 3% of subjects in the active control group (moxifloxacin) and 5% in the placebo arm. The maximum mean PR interval changes relative to the pre-dose baseline value were 25 msec and 34 msec in the two ritonavir-boosted Invirase treatment groups, 1000/100 mg twice daily and 1500/100 mg twice daily, respectively.

Events of syncope/presyncope occurred at a higher than expected rate and were seen more frequently under treatment with saquinavir (11 of 13).

To address the uncertainties regarding the maximum effect seen in this study the MAH computed $ddQTcS_{dense}$ at four additional time points on day 3 (0.25, 1, 14, and 22 hours post-dose). For both

dose schemes a beginning decrease in ddQTcS$_{dense}$ was observed at 22 hours post dose. These data supports the conclusion that maximum increase in ddQTcS$_{dense}$ was seen at 12 hours post-dose for the Invirase/r 1000/100 mg regimen and at 20 hours post-dose for the Invirase/r 1500/100 mg regimen on day 3 (as shown in the Figure 1). It is noted that no pharmacokinetic data are available at this time point. Furthermore the decrease of QT values at 14 hours post dose in all arms hints at the contribution of circadian changes on the size of the overall effect.

Figure 1 Time Course of ddQTcS$_{dense}$ on Day 3 for the Invirase/r 1000/100 mg and 1500/100 mg Treatment Regimens and Moxifloxacin on Day 3



A **post-hoc exploratory PK-PD** analysis of changes in ddQTcS$_{dense}$ as a function of SQV C_{max} suggests a linear relationship between C_{max} and observed QTc increase. These results provide evidence of dose dependence of SQV-induced QTc prolongation. Thus supporting the hypothetical highest risk of QT prolongation and arrhythmias for individual patients during phases of highest drug exposure, such as during the first week of therapy or when concomitant treatment with drugs increasing SQV exposure is initiated.

The results also suggest a predicted C_{max} cutoff value of 8300 ng/ml to maintain the ddQTcS$_{dense}$ below 20 msec. It is noted that the average steady state C_{max} values with the 1000/100 mg bid SQV/r regimen in HIV-infected patients are below this cutoff. However, this was not the case for maximum exposure on day 3 for most of the subjects in the thorough QT/QTc study, and might not apply to HIV-patients initiating SQV/r treatment or concomitant treatment with drugs increasing SQV exposure.

The MAH performed a **post-hoc evaluation of QTc changes** measured at steady state from six SQV/r multiple dose studies to address the limitation of obtaining this information from placebo-controlled studies. One study examined the interaction with methadone in HIV-infected patients and the remaining were in healthy subjects (N=117 to 135). The ECG analysis from the methadone interaction study showed mean QTcB changes at days 7 and 15 as modest with absolute values below 450 msec. This study was assessed during the type II variation, but did not impact on the decision of the contraindication of concomitant use with methadone.

ECG data from the other five studies (MAD study NP21562 and interaction studies with rifabutin, ketoconazole, digoxin and midazolam) in healthy subjects showed that, a SQV/r dose of 1000/100mg given for 2 – 4 weeks, resulted in C_{max} values at 4h roughly between 3000 and 5000ng/ml. ECGs were recorded at different time points from pre-dose, day 1 to day 28, and repeated measurements after the morning dose. No signal for delayed and progressive increases of QT intervals was noted.

Regardless of the methodological limitations (assay sensitivity, etc) of study comparisons, these data provides valuable information and is overall reassuring.

Pharmacokinetic Exposure at Steady State vs Day 3

Saquinavir exposures reach a maximum level on day 3 and decreases 2- to 3-fold between days 3 to 7, with steady-state exposures being approximately 20 to 25% of peak exposure observed on day 3. Steady-state is typically achieved following approximately 10 to 14 days of treatment. This is caused by the inhibition of CYP450 metabolism by SQV/RTV which occurs immediately with the initiation of therapy. However, auto-induction of CYP450 arises after approximately 3 days of treatment, resulting in significantly less metabolic CYP450 inhibition at steady-state.

Previously clinical studies showed that following bid dosing the mean SQV AUC_{0-12} ranged from 14.6 to 39.4 µg·hr/ml and mean SQV C_{max} ranged from 2.16 to 4.9 µg/ml, in HIV-infected patients at steady state conditions. SQV exposure (based on AUC_{0-12} values on day 3) following the Invirase/r 1000/100 mg bid dose in the thorough QTc study (NP21249) was 2.4- to 7.4-fold higher than the exposure seen in HIV patients, while SQV exposure on day 3 following the Invirase/r 1500/100 mg bid dose was 3.5- to 11.0-fold higher Similar results were seen for C_{max}.

It is acknowledged that high AUC values as seen in healthy volunteers may be reached in HIV patients during the first week of SQV/r therapy and whenever concomitant treatment with drugs significantly increasing SQV exposure is started. These periods of high SQV exposure might pose patients at particularly high risk of experiencing an arrhythmic event. In this regard, treatment-naïve patients starting *de novo* on Invirase are considered to be at highest risk for QT prolongation and arrhythmia.

Therefore, the MAH was requested to explore and propose a dosing schedule achieving reduced SQV exposure during the first week of therapy (and especially on day 3), with subsequent dose increase to the recommended dose.

Dosing schedule for treatment naïve patients

A proposal for a modified Invirase/r regimen 500/100 mg bid during the first 7 days followed by the current recommended dose of 1000/100mg bid thereafter for treatment-naïve patients starting *de novo* on Invirase was substantiated with PK-PD modeling based on existing PK data. Based on the PK data from study NP21562 and NP21249 (see table 2) in healthy volunteers exposures on Invirase/r 500/100 mg bid are expected as follows (see table 3).

Table 2. C_{max} and AUC_{0-12} Estimates of SQV following Multiple Dosing of Invirase/r 1000/100 mg and 1500/100 mg Treatment Regimens in Healthy Subjects

Study	**Regimen, N**	**Day**	**C_{max}* (µg/ml)**	**$AUC*_{0-12}$ (µg.h/ml)**	**$C*_{trough}$ (µg/ml)**
NP21562	1000/100, bid, N=3	1 14	4.26 ± 0.16 6.05 ± 1.46	34.6 ± 19.9 36.6 ± 9.66	1.21 ± 0.85** 1.30 ± 0.32**
NP21562	1500/100, bid, N=9	1 14	4.91 ± 2.05 6.75 ± 3.08	42.3 ± 25.2 42.7 ± 20.9	1.69 ± 1.17** 2.06 ± 1.54**
NP21249	1000/100, bid, N= 57	3	11.20 ± 3.26	94.8 ± 30.6	5.94 ± 2.86***
NP21249	1500/100, bid ,N=60	3	15.90 ± 4.36	141± 44.3	9.52 ± 4.14***

*mean ± standard deviation
**12 hour post-dose data from PK Table 2.1 and PK Table 2.3 in the study report NP21562.
***12 hour post-dose data from individual listing of SQV plasma concentrations table reported on CSR NP21249.

Table 3. Projected C_{max}, AUC_{0-12}, and C_{trough} Estimates of SQV following Multiple Dosing of Invirase/r 1000/100 mg bid in Healthy Subjects

Invirase/r Dose	PK Parameter	Day 1	Day 3	Day 7**	Day 14
1000/100 mg bid	C^*_{max} (µg/ml)	3.77	10.90	6.54	5.28
	AUC^*_{0-12} (µg.h/ml)	31.41	94.4	56.64	32.54
	C^*_{trough} (µg/ml)	1.17	6.14	3.68	1.34
500/100 mg, bid					
	C_{max} (µg/ml)	1.89	5.5	3.3	2.64***
	AUC_{0-12} (µg.h/ml)	15.71	47.2	28.3	16.27***
	C_{trough} (µg/ml)	0.59	3.07	1.84	0.67***

*Reported values are mean of mean values after correcting for the dose from studies NP21562 and NP21249.
**Day 7 values are reduced by 40 % from day 3 values, this scaling was based on observed reduction in Ctrough from day 3 to day 7 in study NP21562.
***These values assume continuation of the Invirase/r 500/100 mg bid dose regimen beyond week 1. Because of switching to the Invirase/r 1000/100 mg bid dose regimen at the end of week 1, these values would be higher and expected to approach the 1000/100 mg bid dose regimen values.

Considering that, based on available PK data and on published reports, exposures for Invirase/r 1000/100 mg bid in healthy volunteers are approximately 50% higher compared to HIV infected patients, the estimated exposure data for the reduced dosing is as following (see table 4).

Table 4. Projected C_{max}, AUC_{0-12}, and C_{trough} Estimates of SQV following Multiple Dosing of 500/100 mg bid in HIV-infected Patients

Invirase/r Dose	PK Parameter	Day 1	Day 3	Day 7	Day 14
500/100 mg bid	C_{max} (µg/ml)	1.26	3.67	2.2	1.76*
	AUC_{0-12} (µg.h/ml)	10.48	31.5	18.9	10.85*
	C_{trough} (µg/ml)	0.39	2.04	1.23	0.82*

*These values assume continuation of the Invirase/r 500/100 mg bid dose regimen beyond week 1. Because of switching to the Invirase/r 1000/100 mg bid dose regimen at the end of week 1, these values would be higher and expected to approach the 1000/100 mg bid dose regimen values

Comparison with exposure data obtained earlier with other saquinavir treatment regimens considered effective (Invirase/r 400/400 mg and Fortovase 1200 tid), during the first week of treatment showed that the PK exposure for the projected Invirase/r 500/100 mg is not lower.

Data collected in 84 HIV-infected patients receiving monotherapy with Invirase showed an estimated EC_{50} was 0.05 µg/ml for C_{min} and 3.56 µg.h/ml for AUC_{24h}. The projected C_{min} (or C_{trough}) and AUC_{24h} for the Invirase/r 500/100 mg dose regimen are considerably higher (≥ 4-fold) than these PK-PD model based estimates.

Based on the observed relationship between QTcS vs C_{max} from the QTc study NP21249, the projected maximal increase in QTc on day 3 would be 9 msec for the Invirase/r 500/100 mg bid regimen in treatment-naive patients.

Discussions and conclusions on pharmacology

As discussed above, the MAH provided additional ECG data and PK/PD analyses from the thorough QT/QTc study (study NP21249) and ECG data from several clinical pharmacology studies in healthy volunteers, including the interaction study with methadone evaluated previously.

The additional QTc values from study NP21249, particularly the 22h post dose day 3 values, indicate declining effect on QTc after 12h and 20h for the 1000/100mg and 1500/100mg SQV/r dose, respectively. The post-hoc exploratory PK/PD analysis of changes in ddQTcSdense as a function of C_{max} provides clear evidence of dose dependence of SQV-induced QTc prolongation suggesting a linear relationship between C_{max} and observed QTc increase.

ECG data provided from other clinical pharmacology studies, although with methodological limitations (assay sensitivity, etc), showed no signal for delayed and progressive increases of QT intervals for SQV/r dose of 1000/100mg given for 2 – 4 weeks (C_{max} values at 4h roughly between 3000 and 5000ng/ml). This data provides valuable additional information and is, overall, reassuring.

Overall, no signal for delayed and progressive increases of QT intervals is detectable from the additional analyses provided by the MAH. This supports the hypothetical highest risk of QT prolongation and arrhythmias for individual patients during phases of highest drug exposure, such as during the first week of therapy (as indicated by the results of the thorough QT/QTc study on day 3) or when concomitant treatment with drugs significantly increasing SQV exposure is initiated.

Therefore based on availability of the pharmaceutical form and PK/PD data in healthy volunteers and HIV infected patients a proposal for an initial lower dosing regimen (i.e. 500/100 mg of Invirase/r bid) during the first week in treatment-naïve patients starting treatment with RTV-boosted Invirase (followed by the approved dose of 1000/100mg Invirase/r bid) was deemed acceptable.

Some degree of uncertainty concerning the linearity of the kinetics and the high variability of saquinavir PK is acknowledged. It is agreed that from the safety perspective the proposal is clearly endorsed: a cut-off value for C_{max} of about 8300 ng/ml was predicted to maintain QT prolongation from baseline below 20msec (post-hoc exploratory analysis of study NP21249; Figure 1). With the planned regimen patient exposure will be below this threshold, even if individual exposures were somewhat higher than projected.

Effective therapy in treatment naïve patients is associated with a C_{min} of approximately 0.05 µg/ml and an AUC_{0-24} of about 20 µg·h/ml (EPAR Invirase). Following the MAH's extrapolations C_{trough} and AUC_{0-12} during the first week will be close to these values for almost the whole week (2.04 µg/ml and 31.5 µg·h/ml on day 3 and 1.23 µg/ml and 18.9 µg·h/ml on day 7, respectively). This is further backed up by exposure data obtained with earlier saquinavir treatment regimens considered effective (Invirase/r 400/400mg and Fortovase 1200 tid) that compare well with the calculated exposure during the first week of treatment. Finally, since standard dosing of SQV/r 1000mg/100mg will be started at day 8 plasma levels necessary for full virological suppression should be reached during the second week at the latest.

Therefore the proposed regimen is expected to provide the required safety during the time of treatment initiation together with adequate efficacy in treatment-naïve patients. To further confirm the increased safety (with regards to QT prolongation) with the new regimen while maintaining similar efficacy with regards to the virological suppression, the CHMP requested the MAH to perform a clinical study specifically investigating the PK and QT prolongation in HIV patients initiating *de novo* treatment with SQV/r.

2.2.2. Clinical efficacy

Efficacy overview

Invirase was the first PI approved in 1996 for the treatment of HIV infected adult patients. In 2003 Invirase was recommended to be used only with ritonavir-boosting to address bioavailability issues, in combination with other antiretrovirals. Total patient's exposure to Invirase in the 14 years of marketing, is estimated to be approximately 1 million person years (including approximately 7 years with ritonavir-boosted Invirase). In the last 10 years, with the marketing authorisation of new PIs, the market share for Invirase has been decreasing.

The clinical efficacy of Invirase in combination therapy was demonstrated in two Phase III clinical trials (study SV-14604 and study NV-14256) using clinical endpoints and surrogate markers of viral load and CD4 lymphocyte counts. Similar clinical efficacy and of ritonavir-boosted Invirase in combination

therapy (with two NRTIS/NNRTIs) was demonstrated compared to RTV-boosted Indinavir (study MaxCmin1) and RTV-boosted Lopinavir (study MaxCmin2), based on surrogate markers of viral load and CD4 lymphocyte counts. Both these studies were phase IV open-label.

The GEMINI study compared Invirase/r (1000/100 mg bid) with LPV/r, both given bid, in combination with tenofovir/emtricitabine given once daily, in 337 treatment-naïve participants who were monitored over 48 weeks. Similar levels of viral suppression (64.7% vs. 63.5%) and increases in CD4 counts were seen in both arms. In this study both SQV/r and LPV/r treatment caused an increase from baseline in fasting total cholesterol (TC), LDL cholesterol and triglycerides (TG). Increases from baseline TG were significantly higher for LPV/r.

It is noted that the accepted surrogate marker for progression of cardiovascular disease is cholesterol, while the predictive value of high TG levels is less well established. In a recent analysis of the D:A:D study group (SW Worm, 2010) higher TG levels were marginally independently associated with an increased risk of MI in HIV-positive subjects. However, the extent of the reduction in relative risk (after taking account of latest TC, latest HDL-C and other confounders) suggests that any independent effect is small. The authors concluded that future risk stratification should be focused more closely on non-TG lipids such as total cholesterol and HDL-C and on other and modifiable CVD risk factors including smoking.

Current use of Invirase

Various treatment guidelines recommend Invirase/r as a second-line or alternative RTV-boosted PIs in patients who are intolerant to or have experienced clinical adverse events on other PIs. This was also acknowledged in an Advisory Board meeting convened by the MAH on this topic. It is however noted that other European guidelines still refer to Invirase in first line treatment. As per treatment guidelines, Invirase is also recommended in pregnant women and in children.

As mentioned above the use of Invirase has been declining in the past years with the introduction of other PIs. Most of the use of Invirase is in repeat prescriptions, with very few patients initiating Invirase for the first time.

Invirase will be the first PI to reach patent expiration beginning in November 2010 in the United States and January 2011 in the European Union. The availability of a generic PI may provide an additional treatment option to those without access in the past. The current limited use of Invirase in the developed world might lead to limited demand for generic Invirase in Europe or the United States, however, there is a growing demand for second-line regimens, and thus for PIs, in the developing world.

Discussions and Conclusions on Efficacy

As described above, the efficacy of Invirase in HIV-infected patients in the past 14 years has been demonstrated. Invirase was the first PI approved followed by nine other PIs, some of which are currently considered first line treatment. Invirase has been recognised as currently being recommended in second- or third-line therapy. It is noted that some of the EU guidelines still refer to Invirase as first line treatment. One of the current benefits of Invirase claimed by the MAH is better lipid profile for Invirase *vs* other PIs.

However, there is some uncertainty about this claim since the studies of comparative efficacy and tolerability (MaxCmin1 and MaxCmin2) versus other PIs (Indinavir/r, Lopinavir/r) have some limitations due to their phase IV open label design. In the Gemini study, significantly lower triglyceride levels compared with RTV-boosted lopinavir were observed. Whether this translates into a real clinical benefit is unclear. TG level is not an established surrogate of CV risk lowering in the HIV population. Data from the D.A.D study population analysing relative risk reduction after taking account of latest total cholesterol, HDL-cholesterol and other confounders, suggests that any independent effect is

small. On the other hand the higher pill burden of SQV/r 1000mg/100mg bid treatment might negatively impact treatment compliance.

It was noted that some treatment guidelines recommend off-label use of 2000mg/100mg once daily of SQV/RTV. This regimen is not approved and since it might pose patients at higher risk of arrhythmias due to increased exposure, the warnings in the product information are strengthened to highlight the use of the recommended dose.

2.2.3. Clinical safety

Patient exposure
In the 14 years of marketing experience since approval of Invirase, there have been approximately 1 million person years of exposure to Invirase, including approximately 7 years of experience with RTV-boosted Invirase, in combination with other antiretrovirals. Since approval, post marketing surveillance has not found a causal relationship between Invirase and QT prolongation or TdP.

Considering the already known overall safety profile for Invirase the safety assessment focused on the cardiovascular safety of Invirase particularly on QT and PR prolongation further to the results of the thorough QT/QTc study in healthy volunteers (Study NP21249). The data submitted is summarised and discussed hereafter.

Adverse Events reported in Clinical studies
In the four large randomised clinical trials conducted in HIV patients, one with unboosted Invirase (study NV14256, n=327) and three with RTV-boosted Invirase (MaxCmin1, MaxCmin2, and Gemini studies, n=474), there were no cardiovascular safety signals. However, the number of included subjects is still too small to allow detection of very rare events such as TdP.

According to several publications, the highest risk of TdP is observed in female patients with structural heart disease. It is a limitation of the safety database that patients with cardiac impairment and baseline ECG abnormalities were excluded from the clinical studies. This is reflected in the missing information of the Risk Management Plan.

In the three clinical trials of HIV-infected patients treated with RTV-boosted Invirase for 48 weeks there was no association of cardiac events within the first eight weeks of initiating therapy. The three cardiac events that were reported in the MaxCmin1 and Gemini studies occurred late in study treatment. Based on clinical trial experience, a lack of evidence exists to suggest an association of QT prolongation with RTV-boosted Invirase.

However, the findings of the thorough QTc study conducted in healthy volunteers as discussed earlier in this report (see section 2.2.1 Clinical pharmacology) showed a potential proarrhythmic risk emerging within the first two weeks of treatment due to significantly higher SQV plasma concentrations during this period.

Adverse Events reported Post marketing
The available post marketing adverse events have been examined for evidence of QT/QTc interval prolongation and TdP and for adverse events possibly related to QT/QTc interval prolongation, such as ventricular arrhythmias, cardiac arrest and sudden death.

Table 1 Adverse Events and Co-manifestations of 59 Cases as per MedDRA SMQ Torsades de Pointes as per 21Jul 2009

SOC Abbreviation	High Level Term	Preferred Term	AE	CO	Grand Total
NERV	Disturbances in consciousness NEC	Loss of consciousness	10	3	13
		Syncope	25	1	26
CARD	Ventricular arrhythmias and cardiac arrest	Cardiac arrest	10		10
		Cardio-respiratory arrest	9	1	10
		Torsade de pointes	1		1
		Ventricular arrhythmia	1		1
		Ventricular fibrillation		1	1
		Ventricular tachycardia		1	1
GENRL	Death and sudden death	Sudden death	3		3
INV	ECG investigations	Electrocardiogram qt prolonged	2		2
Total			**61**	**7**	**68**

AE=adverse events; CARD=cardiac CO=co-manifestations; GENRL=general; INV=investigations; NERV=nervous
Source: Table 3 of Drug Safety Report No. 1035313.

There was one death due to TdP reported in 1996 (before RTV was added to boost Invirase) that occurred in a 31 year-old male receiving unboosted Invirase 600 mg tid (lower than current recommendations of Invirase/r of 1000/100 mg bid). The patient had a long and complex clinical history, high viral load and received several concomitant medications (methadone, haloperidol, clindamycin, pyrimethamine, and sulfadiazine) that are known to cause QT prolongation/TdP.

Two other cases of QT prolongation were identified as interactions with other medicinal products known to cause QT prolongation: astemizole (1996; before boosting) and Invirase/r-ciprofloxacin-LPV/r-diltiazem (2007; after boosting).

There were no post marketing experience reports of PR prolongation or AV block ($1^{st,}$ 2^{nd}, 3^{rd} degree) associated with Invirase or concomitant Invirase/r in post-marketing data.

When compared with other RTV-boosted PIs, patient exposure to Invirase is limited. The MAH estimates total exposure to SQV to be about 1 million patient years in 14 years of clinical use (7 years with ritonavir-boosted Invirase). Assuming average duration of SQV use of about 1.5 years, about 670.000 patients have been treated with Invirase.

TdP is a very rare ADR, so its incidence is hard to determine as it also depends on the target population. Incidence of drug-induced TdP was estimated to be in the order of 1:100,000 to 1:220,000 based on studies from Swedish and German Pharmacovigilance databases. Given the low incidence, the low number of arrhythmic events reported for SQV might not be surprising. Underreporting of ADRs is an important limitation of post-marketing reporting, perhaps especially in the context of one of the oldest products being approved for HIV treatment.

Risk Suggested by the thorough QTc Study (NP21249)
As summarised in section 2.2.1 of this report, this study showed the maximum ddQTcS$_{dense}$ for Invirase/r 1000/100 mg bid as 18.86 msec (12 hours) and Invirase/r at 1500/100 mg bid with maximum of 30.22 msec (20 hours), the upper 95% CIs for ddQTcS$_{dense}$ are above 20 msec for both doses.

The supra-therapeutic dose of Invirase/ritonavir appeared to have a greater effect on the **QT interval** than the therapeutic dose of Invirase/ritonavir: 18% and 11% of subjects, respectively, had a QTcS

between 450 and 480 msec. There was no QT prolongation > 500 msec and no torsade de pointes in the study.

In this study, **PR interval prolongation** of > 200 msec was also observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, on Day 3. PR prolongations of > 200 msec were seen in 3% of subjects in the active control group (moxifloxacin) and 5% in the placebo arm.

Events of **syncope/presyncope** occurred at a higher than expected rate and were seen more frequently under treatment with saquinavir (11 of 13).

There was one occurrence of first degree **atrioventricular (AV) block** that resulted in discontinuation of treatment with Invirase/r 1000/100 mg. Maximal increases from the dense pre-dose baseline in the PR interval of +25 msec and +34 msec were seen at 4 hours and 5 hours post-dose for the Invirase/r 1000/100 mg and 1500/100 mg regimens, respectively.

The finding of dose-dependent PR prolongation together with the episode of 1st degree AV block describe true risk of AV block with plasma levels achieved on day 3 in healthy volunteers. The paucity of findings in the post marketing experience suggest that levels achieved with therapeutic doses in HIV-infected patients would only transiently (day 3) reach levels leading to AV block, and that risk diminishes substantially with auto-induction and decreasing plasma concentrations to steady state.

As a consequence of these findings, concomitant use of drugs with potential QT/PR prolongation was contraindicated during the type II variation. Caution was advised for products with the potential to increase SQV exposure and recommendations for monitoring procedures were also introduced in the variation procedure in June 2010.

Risk of QT prolongation and arrhythmia in different patient's population
For patients initiating Invirase for the first time, the highest risk of QT prolongation and associated TdP is expected within the first week of dosing due to significantly higher plasma concentrations of SQV and decrease substantially as SQV plasma levels decline to steady state due to auto-induction (as discussed in section 2.2.1 Clinical pharmacology of this report). Theoretically, the QTc risk is likely to be lower in patients switching from another RTV-boosted PI regimen to a Invirase/r regimen, since these patients would not be expected to have transient PK build-up during the first week of therapy because the metabolizing enzymes are likely to be fully induced in this setting. The QTc risk is expected to be minimal to none in those HIV-infected patients maintained on Invirase/r therapy.

Mitigation factors
In addition to the following measures previously agreed during the type II variation:

- Contraindicated use in patients with congenital or documented acquired QT prolongation, electrolyte disturbances, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias, as well as concurrent therapy with other drugs that prolong the QT and/or PR interval;
- Patients initiating therapy with SQV/r warned of the potential arrhythmogenic risk and told to report any signs of cardiac arrhythmias (e.g., chest palpitations, syncope, presyncope) to their physician. SQV/r to be discontinued in case of significant arrhythmias, QT or PR prolongation;
- Consideration to be given for performing baseline and follow-up ECGs after initiation of treatment in patients with predisposing risk factors or in patients taking concomitant medication known to increase the exposure of saquinavir. An ECG and continuous monitoring should be performed if signs or symptoms suggesting cardiac arrhythmia occur;
- Dissemination of the above mentioned information to the HIV treating physicians and cardiologists via a Dear Health Care Professional Communication in July 2010;

- Additional non-clinical studies to be conducted by the MAH to elucidate the electrophysiological properties of SQV/r for a better understanding of the delayed effect on QT prolongation relative to C_{max} observed in the clinical thorough QT study;

It is now agreed to further amend the Product Information of Invirase to:

- Reduce the dose regimen during the first week of treatment naïve HIV infected patients starting treatment with Invirase in order to address the concern on this population which is considered to be more at risk for QT prolongation and arrhythmias;
- Strengthen the warnings to highlight that the recommended dosing regimen of 1000mg/100mg twice daily (SQV/r) should not be exceeded. This amendment addresses concerns on the identified off-label use of an once daily regimen of 2000mg/100mg (SQV/r) as included in one European guideline;
- Detailed warnings on ECG monitoring considering values of QT interval obtained at baseline are agreed to promote a safe and effective use of Invirase. In this regard there was also agree to add some important information that the physician to give to the patients;

The MAH will also conduct a user testing consultation with target patient groups to evaluate the understanding of the revised Package Leaflet. This user testing is carried out to demonstrate the readability and usefulness of the Package Leaflet to patients.

In addition, and to monitor the impact on the previous measures agreed with regards to the contraindication of concomitant medications commonly used in HIV patients the CHMP requested the MAH to submit a review of these off-label cases. Therefore the MAH will submit specific analyses of reported cases of AEs associated with off-label use of concomitant contraindicated medications within the PSURs. Furthermore, it was agreed that the current PSUR cycle of 3-yearly submission needed to be shortened to guarantee an adequately closely monitoring of the cardiovascular safety of Invirase and of the measures implemented. As a consequence the PSUR cycle is shortened for an annual submission.

Finally, as previously discussed in section 2.2.1 of this report "Clinical Pharmacology", the MAH will perform a clinical study in treatment naïve HIV-1 infected patients starting treatment with Invirase to provide further information on cardiovascular safety any reassurance that this dose regime would increase safety (with regards to QT prolongation) while maintaining similar efficacy.

Conclusions on Safety

Post marketing data has identified one death due to TdP in 1996 (before RTV was added to boost Invirase). This case was confounded by several factors including concomitant medication with products (methadone, haloperidol, clindamycin, pyrimethamine, and sulfadiazine) that are known to cause QT prolongation/TdP. Two other cases of QT prolongation were identified as interactions with known medicinal products to cause QT prolongation: astemizole (1996; before boosting) and Invirase/r-ciprofloxacin-LPV/r-diltiazem interaction (2007; after boosting). There were no post marketing experience reports of PR prolongation or AV block ($1^{st,}$ 2^{nd}, 3^{rd} degree) associated with Invirase or concomitant Invirase/r in post-marketing data.

The thorough QT/QTc Study (NP21249) was conducted to investigate the effect of saquinavir boosted with ritonavir (SQV/r) on the QT interval in healthy volunteers following a publication in *The Lancet* reporting cases of QT prolongation in patients receiving PIs and showing dose dependent blockage of hERG channels *in vitro* for saquinavir, lopinavir, nelfinavir and ritonavir.

The results of this study have demonstrated dose dependent QT and PR prolongation with the therapeutic dose of saquinavir 1000 mg boosted with ritonavir 100 mg bid on day 3 and has identified an average maximum prolongation of QT interval by 18.86 milliseconds (ms) at 12 hours post dose compared to a single dose of moxifloxacin 400 mg of 12.18 ms at 4 hrs post dose. There were no reports of QT prolongation >500 ms nor Torsades de Points (TdP).

The QT prolongation seen in this study was greater than that seen with moxifloxacin control. Dedicated QT studies of other protease inhibitors have not shown such degree of prolongation. However cross-study comparisons should be interpreted with caution due to differences in study drugs, doses chosen, timing of ECG monitoring relative to maximal plasma concentrations, design, conduct and analysis.

Given these findings, the CHMP in June 2010 during the assessment of the type II variation (EMEA/H/C/113/II/085), agreed on several amendments to the Product information (as described above) as a measure to minimise the potential risk in HIV-1 infected patients. In this regard concomitant use with several medicinal products known to cause QT prolongation was contraindicated. However, as it is also known that those medicines are commonly used in the HIV patients, the MAH will submit a specific review on adverse events reported with Invirase in concomitant use with these contraindicated medicinal products. This information will be included within the PSURs that will be submitted annually to allow a closely monitor of this safety issue.

No new safety data has been presented however, considering that patients initiating HIV treatment for the first time are considered to be at higher risk of QT prolongation (and potentially of associated TdP), a reduced dose regimen (in the first week of treatment) for this HIV patients population was agreed as a measure to minimise the risk. The risk of QTc prolongation is likely to be lower in patients switching from another RTV-boosted PI regimen to an Invirase/r regimen, since these patients would not be expected to have transient high exposure during the first week of therapy because the metabolising enzymes are likely to be fully induced in this setting. The QTc risk is expected to be very small to none in HIV-infected patients maintained on Invirase/r therapy.

2.3. Pharmacovigilance

Risk Management Plan (RMP)

A RMP in accordance with the "Guideline on Risk management systems for medicinal products for human use" (EMEA/CHMP/96268/2005) was submitted. This is the first RMP submitted for Invirase.

The table summary of the risk management plan can be found attached to this report.

Periodic Safety Updated Reports (PSURs)

A specific analysis of reported cases of AEs associated with off-label use of concomitant contraindicated medications will be submitted within the PSURs. It was agreed that the current PSUR cycle of 3-yearly submission needed to be shortened to guarantee an adequately close monitoring of the cardiovascular safety of Invirase and of the measures implemented. The PSUR cycle was shortened for an annual submission.

2.4. Product information

The CHMP recommended the amendments to be introduced in the summary of product characteristics (SmPC), Annex II and package leaflet.

As discussed above the CHMP agreed to amend section 4.4 of the SmPC to strengthen the warnings with regards to the recommended dosing regimen of 1000mg/100mg twice daily (SQV/r) not to be exceeded and to provide detailed information on the ECG monitoring considering values of QT interval

obtained at baseline to promote a safer and effective use of Invirase with regards to the risk of QT prolongation. Section 4.2 was amended to reflect the reduced dosing regimen agreed during the first week of treatment-naïve patients staring on Invirase.

The relevant sections of the PL were amended in line with the changes agreed for the SmPC.

Annex II is amended to reflect that a Risk Management Plan was submitted and agreed, that the PSUR cycle is shortened for 1-yearly submission (as explained above) and finally to state the commitment made for a study with the modified SQV/r regimen in treatment naïve HIV patients (to study QT-prolongation, PK, antiviral activity) to be performed and that the protocol will be submitted for CHMP agreement.

3. Overall discussion and benefit/risk assessment

The efficacy of saquinavir/r in HIV-infected patients has been demonstrated in the past 14 years. Invirase was the first PI being approved in 1996 followed by other nine PIs which are currently considered in first line treatment. Invirase has been recognised as currently being used in second- or third-line therapy as an alternative PI in patients who are intolerant to or have experienced clinical adverse events (e.g. diarrhea) or laboratory abnormalities (e.g. increased liver function tests or lipid levels).

There is some uncertainty about the superior tolerability and better lipid profile claimed for Invirase compared to other PIs since the studies of comparative efficacy and tolerability for saquinavir versus other PIs (indinavir, lopinavir) have some limitations due to their design and compliance to treatment (higher pill burden of SQV/r 1000mg/100mg bid). However, some European guidelines refer Invirase in first line treatment. Also the off-label use of saquinavir/r 2000mg/100mg once daily is referred in treatment guidelines.

Results of a thorough QT/QTc study (NP 21249) in healthy volunteers demonstrated dose dependent QT and PR prolongation with the therapeutic dose of saquinavir 1000 mg boosted with ritonavir 100 mg bid on day 3 and has identified an average maximum prolongation of QT interval by 18.86 milliseconds (ms) at 12 hours post dose compared to a single dose of moxifloxacin 400 mg of 12.18 ms at 4 hrs post dose. There were no reports of QT prolongation >500 ms nor Torsades de Points (TdP) in this study. There was one case of first degree atriovascular (AV) block that resulted in discontinuation of treatment.

The QT prolongation seen in this study was greater than that seen with moxifloxacin control. Dedicated QT studies of other protease inhibitors have not shown such degree of prolongation. However cross-study comparisons should be interpreted with caution due to differences in study drugs, doses chosen, timing of ECG monitoring relative to maximal plasma concentrations, design, conduct and analysis.

The MAH provided additional ECG data and PK/PD analyses from the thorough QT/QTc study and ECG data from several clinical pharmacology studies.

The additional QTc values from study NP21249, indicate declining effect on QTc after 12h and 20h for the 1000/100mg and 1500/100mg SQV/r dose, respectively. The post-hoc exploratory PK/PD analysis provides evidence of dose dependence of SQV-induced QTc prolongation suggesting a linear relationship between C_{max} and observed QTc increase. ECG data provided from other clinical pharmacology studies, although with methodological limitations, showed no signal for delayed and progressive increases of QT intervals for SQV/r dose of 1000/100mg given for 2 – 4 weeks. Overall, no signal for delayed and progressive increases of QT intervals is detectable from the additional analyses provided.

The hypothetical highest risk of QT prolongation and arrhythmias for individual patients during phases of highest drug exposure, such as during the first week of therapy (as indicated by the results of the thorough QT/QTc study on day 3) or when concomitant treatment with drugs significantly increasing SQV exposure is initiated, was confirmed by the additional PK-PD data submitted.

No new safety data was presented during this review. Post marketing data identified one death due by TdP in 1996 (before RTV was added to boost Invirase). This case was confounded by several factors including concomitant medication with products (methadone, haloperidol, clindamycin, pyrimethamine, and sulfadiazine) that are known to cause QT prolongation/TdP and are now contraindicated. Two other cases of QT prolongation were identified as interactions with known medicinal products to cause QT prolongation: astemizole (1996; before boosting) and Invirase/r-ciprofloxacin-LPV/r-diltiazem interaction (2007; after boosting). There were no post marketing experience reports of PR prolongation or AV block ($1^{st,}$ 2^{nd}, 3^{rd} degree) associated with Invirase or concomitant Invirase/r in post-marketing data. Overall, no cardiovascular signal was detected from post-marketing data but the patients exposure has been rather limited (compared with other PIs) and underreporting or misclassification cannot be excluded. The comparison of saquinavir/r with more recent and frequently prescribed PIs like lopinavir/r or atazanavir, which showed a small signal in QT studies but reported more cases of TdP during post marketing, is difficult.

Based on the above the MAH submitted PK/PD data in healthy volunteers and HIV infected patients to support an initial lower dosing regimen (i.e. 500/100 mg of Invirase/r bid) during the first week in treatment-naïve patients starting treatment with RTV-boosted Invirase (followed by the approved dose of 1000/100mg Invirase/r bid) as a measure to minimise the risk for QT prolongation identified for this group of patients considered to be at highest risk.

The proposed regimen is expected to provide the required safety during the time of treatment initiation together with adequate efficacy in treatment-naïve patients. To further confirm the increased safety (with regards to QT prolongation) with the newly regimen while maintaining similar efficacy, the CHMP requested the MAH to perform a clinical study specifically investigating the PK and QT prolongation in HIV patients initiating *de novo* treatment with SQV/r. The study protocol will be submitted to the CHMP for review and agreement.

In addition, and considering that contraindications for concomitant use of Invirase with QT prolonging medicinal products are already in place, the CHMP agreed on the need for the MAH to specifically report in PSURs off-label cases with concomitant use of Invirase with these recently contraindicated medicinal products. To allow this close monitoring the PSUR cycle has been shortened for yearly submission.

Furthermore, the CHMP agreed to detailed recommendations for ECG monitoring in the SmPC in view of the fact that the risk for QT prolongation is different for patients starting treatment with Invirase/r than for patients stable on Invirase/r treatment. For patients demonstrating a clinically relevant increase in QT interval with concomitant therapy, either RTV-boosted Invirase or the concomitant therapy or both should be discontinued. To address the fact that there are treatment guidelines that recommend off-label dosing of SQV/rtv 2000/100mg once daily and that this regimen, not being approved, might pose patients at higher risk of arrhythmias due to increased exposure, the CHMP agreed to strengthen the warnings on cardiovascular risks to clearly mention that the recommended dose should not be exceed.

Benefit/risk balance

Taken this into account, the benefit/risk balance for Invirase is considered favourable for HIV-1 infected patients in accordance with the above mentioned recommendations.

4. Overall conclusion

Having reviewed the overall data provided by the MAH in writing the CHMP concluded that benefit still outweighs the risks for patients treated with Invirase. However, the CHMP recommended that treatment-naïve patients starting on Invirase should take a reduced dose of saquinavir/r during the first week of treatment.

The CHMP also concluded that the Product Information for Invirase should provide further detailed information of cardiac safety monitoring and strengthen the warning that the recommended dose for Invirase should not be exceeded. Therefore, the CHMP recommended the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflet.

Furthermore, a Risk Management Plan has been agreed for Invirase including the additional pharmacovigilance activity for the MAH to perform a clinical study to determine the effect of the modified SQV/r (saquinavir-boosted by ritonavir) regimen (500/100 mg for the 1st week followed by 1000/100 mg for the 2nd week) on the QTc interval, pharmacokinetics and in HIV-1 infected patients. An increased frequency of submission of PSURs and the standard readability testing to evaluate the understanding of the revised Package Leaflet Submission as routine measure to minimise the risk were also included in the Risk Management Plan.

Therefore, the CHMP recommended the variation of the Marketing Authorisation for Invirase for which the revised Summary of Product Characteristics, Annex II and Package Leaflet are set out respectively in annexes I, II and IIIB of the Opinion.

The scientific conclusions and the grounds for the amendment of the SPC, Annex II, and package leaflet are set out in Annex IV of the opinion.

Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below (see letter of undertaking attached to this report):

Area[1]	Description	Due date
Clinical	Following procedure EMEA/H/C/113/A-20/0088: Phase I study NP 25607 entitled "*To determine the effect of the modified SQV/r (saquinavir-boosted by ritonavir) regimen (500/100 mg for the 1st week followed by 1000/100 mg for the 2nd week) on the QTc interval, pharmacokinetics and antiviral activity in HIV-1 infected patients.*" Submission of Protocol Submission of final CSR	 09/02/2011 30/09/2013*
Pharmacovigilance	Following procedure EMEA/H/C/113/A-20/0088: Product Information: Report the results of a readability testing to evaluate the understanding of the text of the revised Package Information Leaflet.	 30/04/2011
Pharmacovigilance	Following procedure EMEA/H/C/113/A-20/0088: Evaluate the frequency of contraindicated concomitant medications in spontaneous Adverse Drug Reaction (ADR)	 30/01/2011

	reports in the next PSUR and future PSURs and to evaluate the adverse events (AEs) associated with the off-label use of contraindicated concomitant medications.	

[1.] Quality, Pre-clinical, Clinical, Pharmacovigilance
* Due date subject to change following CHMP assessment and agreement on protocol.

5. Conclusion and grounds for the recommendation

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Invirase initiated by the European Commission.
- The Committee reviewed all preclinical and clinical efficacy and safety data submitted by the MAH in relation to the cardiovascular risk of Invirase;
- The Committee confirmed the evidence of dose dependence of SQV-induced QTc prolongation suggesting a linear relationship between the maximum concentration and observed QTc increase. Therefore, a higher risk of QT prolongation and arrhythmias for individual patients during phases of highest exposure of the product, such as during the first week of therapy;
- The Committee, considering pharmacokinetic/pharmacodynamic data in healthy volunteers and HIV infected patients, concluded on an initial lower dosing regimen (i.e. 500/100 mg of Invirase/r twice a day) during the first week in treatment-naïve patients starting treatment with RTV-boosted Invirase;
- The CHMP concluded that the Product Information for Invirase should further detail the precautions for use with regards to the monitoring of the ECG and strengthen the warning that the recommended dose for Invirase should not be exceed. A Risk Management Plan has been agreed for Invirase including a clinical study to determine the effect of the modified saquinavir-boosted by ritonavir reduced dose regimen (500/100 mg for the 1st week followed by 1000/100 mg for the 2nd week) on the QTc interval and pharmacokinetics in HIV-1 infected patients. The increase frequency of the submission of PSURs on a yearly basis was also included in the Risk Management Plan.
- The Committee, as a consequence, concluded that benefit still outweighs the risks in the currently authorised therapeutic indication for Invirase.

Table Summary of the EU Risk Management Plan

Safety Concern	Proposed PV Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important identified risks		
QT prolongation,TdP, ventricular arrhythmias, sudden death, syncope	Routine Pharmacovigilance Activity: Continue routine pharmacovigilance: Monitoring of signs and symptoms of arrhythmias Additional Pharmacovigilance Activity: - Conduct three preclinical studies to understand potential mechanisms for QT prolongation - Propose open label clinical study in treatment naïve HIV infected patients initiating antiretroviral therapy with Invirase/r at 500mg/100 mg bid for days 1-7 and then 1000mg/100mg bid days 8-14. PK, ECGs and virological supression would be assessed - Evaluate frequency of contraindicated concomitant medications in spontaneous ADR reports in the next PSUR and future PSURs and to	Routine Risk Minimisation Activity: - Standard readability testing to evaluate understanding of the revised Package Leaflet - Submission of yearly PSURs, unless otherwise specified by the CHMP - Rewording/improving sections of the Invirase SmPC to ensure physician receipt and understanding of relevant information, including a proposed reduced starting dose of Invirase during first week of treatment for treatment-naive patients initiating treatment with Invirase/ritonavir in SmPC/PL: *Section 4.2 Posology and method of administration – Adults and adolescents over the age of 16 years:* *For treatment-naive patients initiating treatment with Invirase/ritonavir, the recommended starting dose of Invirase is 500 mg (1 x 500 mg film-coated tablet) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents for the first 7 days of treatment (see Summary of Product Characteristics for INVIRASE 500 mg film-coated tablets). After 7 days, the recommended dose of Invirase is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. Patients switching immediately from treatment with another protease inhibitor taken with ritonavir or from a non-nucleoside reverse transcriptase inhibitor based regimen, without a wash-out period, should however initiate and continue Invirase at the standard recommended dose of 1000 mg two times daily with ritonavir 100 mg two times daily.* *Section 4.4 Special warnings and precautions for use:* *- Cardiac conduction and repolorasiation abnormalities: Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted Invirase (see section 5.1). Concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is therefore contraindicated (see section 4.3).*

	evaluate the events associated with them. A decrease in the frequency of such obervations over time might be an appropriate additional criterion.	*Since the magnitude of QT and PR prolongation increases with increasing concentrations of saquinavir, the recommended dose of ritonavir-boosted Invirase should not be exceeded. Ritonavir-boosted Invirase at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended. Other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution.* *Women and elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval.* *- <u>Clinical Management</u>:* *Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval.* *Patients initiating therapy with ritonavir-boosted Invirase:* *- An ECG should be performed prior to initiation of treatment: patients with a QT interval > 450 msec should not use ritonavir-boosted Invirase.* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy. Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.* *Patients stable on ritonavir-boosted Invirase and requiring concomitant medication with potential to increase the the exposure of saquinavir or patients on medication with potential to increase the exposure of saquinavir and requiring concomitant ritonavir-boosted Invirase where no alternative therapy is available and the benefits outweigh the risks:* *- An ECG should be performed prior to initiation of the concomitant therapy: patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5).*

		- For patients with a baseline QT interval < 450 msec, an on-treatment ECG should be performed. For patients demonstrating a subsequent increase in QT-interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Invirase or the concomitant therapy or both. *- <u>Essential Patient Information</u>:* *- Prescribers must ensure that patients are fully informed regarding the following information on cardiac conduction and repolarisation abnormalities:* *- Patients initiating therapy with ritonavir boosted Invirase should be warned of the arrhythmogenic risk associated with QT and PR prolongation and told to report any sign or symptom suspicious of cardiac arrhythmia (e.g., chest palpitations, syncope, presyncope) to their physician.* *- Physicians should inquire about any known familial history of sudden death at a young age as this may be suggestive of congenital QT prolongation.* *- Patients should be advised of the importance not to exceed the recommended dose.* *- Each patient (or patient's caregiver) should be reminded to read the Package Leaflet included in the Invirase Package.* - Rewording of sections of the Invirase Package Leaflet to ensure patient receipt and understanding of relevant information: *Do not take Invirase* *• if you are allergic (hypersensitive) to saquinavir, ritonavir or any of the other ingredients (see section "Important information about an ingredient of Invirase" and section "What Invirase contains").* *• if you were born with or have* *- any condition with certain abnormal electrocardiogram (ECG, electrical recording of the heart) changes,* *- a salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment,* *- a very slow heart rate (bradycardia),* *- a weak heart (heart failure), or* *- a history of abnormal heart rhythms (arrhythmias)* *• if you are taking other medicines that result in certain abnormal ECG changes:* *- certain HIV antiviral agents (e.g. atazanavir, lopinavir),* *- certain heart medicines (amiodarone, bepridil, dofetilide, flecainide,*

		hydroquinidine, ibutilide, lidocaine, propafenone, quinidine, sotalol), *- medicines to treat depression (amitryptiline, impramine, trazodone),* *- medicines used to treat severe mental disorders (e.g. clozapine, haloperidol, mesoridazine, phenothiazines, sertindole, sultopride, thioridazine, ziprasidone),* *- certain anti-infectives (e.g. clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin)* *- certain narcotic analgesics (e.g. methadone),* *- medicines used to treat erectile dysfunction (sildenafil, vardenafil, tadalafil),* *- some other medicines (alfentanyl, cisapride, dapsone, diphemanil, disopyramide,* *fentanyl, mizolastine, quinine, vincamine)* *Abnormal heart rhythms (arrhythmias):* *Invirase can change your heart's ECG, especially if you are female or elderly. If you are taking any medicine that decreases your blood potassium levels talk to your doctor before taking Invirase. Contact your doctor immediately, if you experience palpitations or an irregular heartbeat during treatment. He/she may wish to perform an ECG to measure your heart rhythm.* *How To Take Invirase:* *If you have not received other HIV medicines before and you are taking Invirase for the first time, you should take a reduced dosage of Invirase of one 500 mg film coated tablet with one 100 mg capsule of Norvir (ritonavir) two times daily for the first week (see Package Leaflet for INVIRASE 500 mg film-coated tablets). After the first week you should continue with the standard Invirase dosage of five 200 mg capsules with one 100 mg capsule of Norvir (ritonavir) two times daily. Patients who switch immediately without pause between the treatment regimens from another protease inhibitor in combination with Norvir (ritonavir) or from a non-nucleoside reverse transcriptase inhibitor based regimen should initiate and continue with the standard recommended dosage of Invirase of five 200 mg capsules two times daily with ritonavir 100 mg two times daily.* - More specific guidance on ECG monitoring to be included in Warnings and Precautions in the SmPC: • *Clinical Management:* *Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking*

		concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval. *Patients initiating therapy with ritonavir-boosted Invirase:* *- An ECG should be performed prior to initiation of treatment: patients with a QT interval > 450 msec should not use ritonavir-boosted Invirase.* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy. Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.* *Patients stable on ritonavir-boosted Invirase and requiring concomitant medication with potential to increase the the exposure of saquinavir or patients on medication with potential to increase the exposure of saquinavir and requiring concomitant ritonavir-boosted Invirase where no alternative therapy is available and the benefits outweigh the risks:* *- An ECG should be performed prior to initiation of the concomitant therapy: patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5).* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG should be performed. For patients demonstrating a subsequent increase in QT-interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Invirase or the concomitant therapy or both.* - Modified wording in SmPC to highlight importance of not exceeding the recommended doses: *Since the magnitude of QT and PR prolongation increases with increasing concentrations of saquinavir, the recommended dose of ritonavir-boosted Invirase should not be exceeded. Ritonavir-boosted Invirase at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended. Other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution.*

		- Contraindications in new labeling for *congenital or documented acquired QT prolongation, electrolyte disturbances particularly uncorrected hypokalaemia, clinically relevant bradycardia,* *clinically relevant heart failure with reduced left-ventricular fraction, and previous history of symptomatic arrhythmias* - New labeling restrictions with all drugs having QT prolongation contraindicated (implemented as per Type II Variation Application EMEA/H/C/000113/ II/0085): *Invirase is contraindicated in patients with: concurrent therapy with drugs that prolong QT and/or PR interval (see sections 4.4 and 4.5).* *Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving Invirase/ritonavir (see sections 4.3, 4.4 and 5.1), additive effects on QT and PR interval prolongation may occur. Therefore, concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated. The combination of Invirase/ritonavir with drugs known to increase the exposure of saquinavir is not recommended and should be avoided when alternative treatment options are available. If concomitant use is deemed necessary because the potential benefit to the patient outweighs the risk, particular caution is warranted (see section 4.4; for information on individual drugs, see Table 1).*
PR prolongation	Routine Pharmacovigilance Activity: Continue routine pharmacovigilance; Monitoring of signs and symptoms of arrhythmias <u>Additional Pharmacovigilance Activity</u>: - Conduct three preclinical studies to understand potential mechanisms for QT prolongation - Propose open label clinical study in treatment naïve HIV infected patients	<u>Routine Risk Minimisation Activity</u>: - Standard readability testing to evaluate understanding of the revised Package Leaflet - Submission of yearly PSURs, unless otherwise specified by the CHMP - Rewording/improving sections of the Invirase SmPC to ensure physician receipt and understanding of relevant information, including a proposed reduced starting dose of Invirase during first week of treatment for treatment-naive patients initiating treatment with Invirase/ritonavir in SmPC/PL: *<u>Section 4.2 Posology and method of administration – Adults and adolescents over the age of 16 years</u>:* *For treatment-naive patients initiating treatment with Invirase/ritonavir, the recommended starting dose of Invirase is 500 mg (1 x 500 mg film-coated tablet) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents for the first 7 days of treatment (see Summary of Product Characteristics for INVIRASE 500 mg film-coated tablets). After 7 days,*

	initiating antiretroviral therapy with Invirase/r at 500mg/100 mg bid for days 1-7 and then 1000mg/100mg bid days 8-14. PK, ECGs and virological supression would be assessed - Evaluate frequency of contraindicated concomitant medications in spontaneous ADR reports in the next PSUR and future PSURs and to evaluate the events associated with them. A decrease in the frequency of such obervations over time might be an appropriate additional criterion.	*the recommended dose of Invirase is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. Patients switching immediately from treatment with another protease inhibitor taken with ritonavir or from a non-nucleoside reverse transcriptase inhibitor based regimen, without a wash-out period, should however initiate and continue Invirase at the standard recommended dose of 1000 mg two times daily with ritonavir 100 mg two times daily.* *Section 4.4 Special warnings and precautions for use* *- <u>Cardiac conduction and repolorasiation abnormalities</u>: Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted Invirase (see section 5.1). Concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is therefore contraindicated (see section 4.3).* *Since the magnitude of QT and PR prolongation increases with increasing concentrations of saquinavir, the recommended dose of ritonavir-boosted Invirase should not be exceeded. Ritonavir-boosted Invirase at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended. Other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution.* *Women and elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval.* *- <u>Clinical Management</u>:* *Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval.* *Patients initiating therapy with ritonavir-boosted Invirase:* *- An ECG should be performed prior to initiation of treatment: patients with a QT*

		interval > 450 msec should not use ritonavir-boosted Invirase. *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy. Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.* *Patients stable on ritonavir-boosted Invirase and requiring concomitant medication with potential to increase the the exposure of saquinavir or patients on medication with potential to increase the exposure of saquinavir and requiring concomitant ritonavir-boosted Invirase where no alternative therapy is available and the benefits outweigh the risks:* *- An ECG should be performed prior to initiation of the concomitant therapy: patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5).* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG should be performed. For patients demonstrating a subsequent increase in QT-interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Invirase or the concomitant therapy or both.* *- <u>Essential Patient Information</u>:* *- Prescribers must ensure that patients are fully informed regarding the following information on cardiac conduction and repolarisation abnormalities:* *- Patients initiating therapy with ritonavir boosted Invirase should be warned of the arrhythmogenic risk associated with QT and PR prolongation and told to report any sign or symptom suspicious of cardiac arrhythmia (e.g., chest palpitations, syncope, presyncope) to their physician.* *- Physicians should inquire about any known familial history of sudden death at a young age as this may be suggestive of congenital QT prolongation.* *- Patients should be advised of the importance not to exceed the recommended dose.* *- Each patient (or patient's caregiver) should be reminded to read the Package Leaflet included in the Invirase Package.* - Rewording of sections of the Invirase Package Leaflet to ensure patient receipt and understanding of relevant information: *Do not take Invirase*

		• if you are allergic (hypersensitive) to saquinavir, ritonavir or any of the other ingredients (see section "Important information about an ingredient of Invirase" and section "What Invirase contains"). *• if you were born with or have* *- any condition with certain abnormal electrocardiogram (ECG, electrical recording of the heart) changes,* *- a salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment,* *- a very slow heart rate (bradycardia),* *- a weak heart (heart failure), or* *- a history of abnormal heart rhythms (arrhythmias)* *• if you are taking other medicines that result in certain abnormal ECG changes:* *- certain HIV antiviral agents (e.g. atazanavir, lopinavir),* *- certain heart medicines (amiodarone, bepridil, dofetilide, flecainide, hydroquinidine, ibutilide, lidocaine, propafenone, quinidine, sotalol),* *- medicines to treat depression (amitryptiline, impramine, trazodone),* *- medicines used to treat severe mental disorders (e.g. clozapine, haloperidol, mesoridazine, phenothiazines, sertindole, sultopride, thioridazine, ziprasidone),* *- certain anti-infectives (e.g. clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin)* *- certain narcotic analgesics (e.g. methadone),* *- medicines used to treat erectile dysfunction (sildenafil, vardenafil, tadalafil),* *- some other medicines (alfentanyl, cisapride, dapsone, diphemanil, disopyramide,* *fentanyl, mizolastine, quinine, vincamine)* *Abnormal heart rhythms (arrhythmias):* *Invirase can change your heart's ECG, especially if you are female or elderly. If you are taking any medicine that decreases your blood potassium levels talk to your doctor before taking Invirase. Contact your doctor immediately, if you experience palpitations or an irregular heartbeat during treatment. He/she may wish to perform an ECG to measure your heart rhythm.* *How To Take Invirase:* *If you have not received other HIV medicines before and you are taking Invirase for the first time, you should take a reduced dosage of Invirase of one 500 mg film coated tablet with one 100 mg capsule of Norvir (ritonavir) two times daily*

		for the first week (see Package Leaflet for INVIRASE 500 mg film-coated tablets). After the first week you should continue with the standard Invirase dosage of five 200 mg capsules with one 100 mg capsule of Norvir (ritonavir) two times daily. Patients who switch immediately without pause between the treatment regimens from another protease inhibitor in combination with Norvir (ritonavir) or from a non-nucleoside reverse transcriptase inhibitor based regimen should initiate and continue with the standard recommended dosage of Invirase of five 200 mg capsules two times daily with ritonavir 100 mg two times daily. - More specific guidance on ECG monitoring to be included in Warnings and Precautions in the SmPC: • *Clinical Management:* *Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval.* *Patients initiating therapy with ritonavir-boosted Invirase:* *- An ECG should be performed prior to initiation of treatment: patients with a QT interval > 450 msec should not use ritonavir-boosted Invirase.* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy. Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.* *Patients stable on ritonavir-boosted Invirase and requiring concomitant medication with potential to increase the the exposure of saquinavir or patients on medication with potential to increase the exposure of saquinavir and requiring concomitant ritonavir-boosted Invirase where no alternative therapy is available and the benefits outweigh the risks:* *- An ECG should be performed prior to initiation of the concomitant therapy: patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5).* *- For patients with a baseline QT interval < 450 msec, an on-treatment ECG*

		should be performed. For patients demonstrating a subsequent increase in QT-interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Invirase or the concomitant therapy or both. - Modified wording in SmPC to highlight importance of not exceeding the recommended doses: *Since the magnitude of QT and PR prolongation increases with increasing concentrations of saquinavir, the recommended dose of ritonavir-boosted Invirase should not be exceeded. Ritonavir-boosted Invirase at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended. Other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution.* - Contraindications in new labeling for *congenital or documented acquired QT prolongation, electrolyte disturbances particularly uncorrected hypokalaemia, clinically relevant bradycardia,* *clinically relevant heart failure with reduced left-ventricular fraction, and previous history of symptomatic arrhythmias* - New labeling restrictions with all drugs having QT prolongation contraindicated (implemented as per Type II Variation Application EMEA/H/C/000113/ II/0085): *Invirase is contraindicated in patients with: concurrent therapy with drugs that prolong QT and/or PR interval (see sections 4.4 and 4.5.)* *Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving Invirase/ritonavir (see sections 4.3, 4.4 and 5.1), additive effects on QT and PR interval prolongation may occur. Therefore, concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated. The combination of Invirase/ritonavir with drugs known to increase the exposure of saquinavir is not recommended and should be avoided when alternative treatment options are available. If concomitant use is deemed necessary because the potential benefit to the patient outweighs the risk, particular caution is warranted (see section 4.4; for information on individual drugs, see Table 1).*
Important Potential		

Risks – Interactions		
Ritonavir	Routine pharmacovigilance	Warning included in SmPC, section 4.4: *<u>Interaction with ritonavir</u>:* *The recommended dose of Invirase and ritonavir is 1000 mg Invirase plus 100 mg ritonavir twice daily. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse events. Co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.*
Rifampicin	Routine pharmacovigilance	Rifampicin is contraindicated in combination with Invirase/ritonavir, which is included in SmPC, section 4.3: "Rifampicin *(risk of severe hepatocellular toxicity) (see sections 4.4, 4.5, and 4.8)"*
Rifabutin	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5, for different regimens of rifabutin
Efavirenz	Routine pharmacovigilance	Warning is included in SmPC, section 4.4: *<u>Interaction with efavirenz:</u>* *The combination of saquinavir and ritonavir with efavirenz has been shown to be associated with an increased risk of liver toxicity; liver function should be monitored when saquinavir and ritonavir are co-administered with efavirenz. No clinically significant alterations of either saquinavir or efavirenz concentration were noted in studies in healthy volunteers or in HIV-infected patients (see section 4.5).* Specific recommendations concerning co-administration are provided in SmPC, section 4.5
St. John's Wort	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Herbal preparations containing St. John's wort must not be used concomitantly with Invirase. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible saquinavir levels. Saquinavir levels may increase on stopping St. John's wort, and the dose of saquinavir may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.*
Garlic capsules	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Patients on saquinavir treatment must not take garlic capsules due to the risk of*

		decreased plasma concentrations and loss of virological response and possible resistance to one or more components of the antiretroviral regimen.
HMG-CoA reductase inhibitors	Routine pharmacovigilance	Warning is included in SmPC, section 4.4: *Interaction with HMG-CoA reductase inhibitors:* *Caution must be exercised if Invirase/ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).*
Oral contraceptives	Routine pharmacovigilance	Warning is included in SmPC, section 4.4: *Oral contraceptives:* *Because concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir, alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered (see section 4.5).*
Tipranavir	Routine pharmacovigilance	Warning is included in SmPC, section 4.4: *Interaction with tipranavir: Concomitant use of boosted saquinavir and tipranavir, co-administered with low dose ritonavir in a dual-boosted regimen, results in a significant decrease in saquinavir plasma concentrations (see section 4.5). Therefore, the co-administration of boosted saquinavir and tipranavir, co-administered with low dose ritonavir, is not recommended.*
Digoxin	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Caution should be exercised when Invirase/ritonavir and digoxin are co-administered. The serum concentration of digoxin should be monitored and a dose reduction of digoxin should be considered if necessary.*
Trazodone	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).*
Ketoconazole	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *No dose adjustment required when saquinavir/ritonavir combined with ≤ 200 mg/day ketoconazole. High doses of ketoconazole (> 200 mg/day) are not recommended.*
Methadone	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC,

		section 4.5: *Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).*
Midazolam	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Co-administration of Invirase/ritonavir with orally administered midazolam is contraindicated (see section 4.3). Caution should be used with co-administration of Invirase and parenteral midazolam.* *If Invirase is co-administered with parenteral midazolam it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment should be considered, especially if more than a single dose of midazolam is administered.* Contraindication is included in SmPC, section 4.3: *Invirase is contraindicated in patients with:* *midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5).*
Omeprazole	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Combination not recommended.*
Triazolam	Routine pharmacovigilance	Contraindication is included in SmPC, section 4.3: *Invirase is contraindicated in patients with:* *….triazolam (potential for prolonged or increased sedation, respiratory depression)* Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *Contraindicated in combination with saquinavir/ritonavir, due to the risk of potentially prolonged or increased sedation and respiratory depression (see section 4.3).*
Ergot alkaloids	Routine pharmacovigilance	Specific recommendations concerning co-administration are provided in SmPC, section 4.5: *The concomitant use of Invirase/ritonavir and ergot alkaloids is contra-indicated (see section 4.3).* Contraindication is included in SmPC, section 4.3:

		Invirase is contraindicated in patients with: *…ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (potential for acute ergot toxicity)*
Glucocorticoids	Routine pharmacovigilance	Warning is included in SmPC, section 4.4: *Glucocorticoids:* *Concomitant use of boosted saquinavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).*
Food	Routine pharmacovigilance	SmPC, section 4.2, contains the following recommendation: *Invirase capsules should be swallowed whole and taken at the same time as ritonavir with or after food (see section 5.2).*
Important Potential Risks - Class Effects		
Increase in fat redistribution or lipodystrophy	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; listed as a warning in SmPC, sections 4.4 and 4.8: *Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).* *Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump).*
Increase in osteonecrosis thought to be multifactorial	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; listed as a warning in SmPC, section 4.4: *Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV–disease and/or long-term exposure to combination antiretroviral therapy*

		(CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.
Direct or indirect harmful effects to the embryo or foetus in pregnant mothers or congenital birth defects or infants exposed to saquinavir during nursing.	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; SmPC, section 4.6, contains a corresponding warning: *Pregnancy: Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and post-natal development. Clinical experience in pregnant women is limited: Congenital malformations, birth defects and other disorders (without a congenital malformation) have been reported rarely in pregnant women who had received saquinavir in combination with other antiretroviral agents. However, so far the available data are insufficient and do not identify specific risks for the unborn child. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3).* *Lactation: There are no laboratory animal or human data available on secretion of saquinavir in breast milk. The potential for adverse reactions to saquinavir in nursing infants cannot be assessed, and therefore, breast-feeding should be discontinued prior to receiving saquinavir. It is recommended that HIV-infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.*

Increased risk for severe and potentially fatal hepatic adverse events in patients with Hepatitis B or C or decompensated liver disease	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; SmPC, Contraindications: *Invirase is contraindicated in patients with decompensated liver disease*; and section 4.4 contains a corresponding warning: *The safety and efficacy of saquinavir/ritonavir has not been established in patients with significant underlying liver disorders, therefore saquinavir/ritonavir should be used cautiously in this patient population. Invirase/ritonavir is contraindicated in patients with decompensated liver disease (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.* *Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.* *No dosage adjustment seems warranted for patients with moderate hepatic impairment based on limited data. Close monitoring of safety (including signs of cardiac arrhythmia) and of virologic response is recommended due to increased variability of the exposure in this population (see sections 4.2 and 5.2). There have been reports of exacerbation of chronic liver dysfunction, including portal hypertension, in patients with underlying hepatitis B or C, cirrhosis and other underlying liver abnormalities.*
Increased bleeding and skin haematomas and haemarthrosis in haemophilics type A and B treated with protease inhibitors	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; the SmPC, section 4.4, contains a corresponding warning: *There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding*.
Increased new onset diabetes mellitus and	Close observation through routine pharmacovigilance	No particular risk minimization activity is considered necessary; the SmPC, section 4.4, contains a corresponding warning:

hyperglycemia in patients with protease inhibitors.	system.	*New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these patients, the hyperglycaemia was severe and in some cases was also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.*
Risk of Immune Reactivation Syndrome in patients with severe immune deficiency at the time of institution of combination antiretroviral therapy.	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; the SmPC, section 4.4, contains a corresponding warning: *In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.*
Renal toxicity	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary, the SmPC section 4.4, contains a corresponding warning: *Renal clearance is only a minor elimination pathway, the principal route of metabolism and excretion for saquinavir being via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing saquinavir/ritonavir in this population.*
Hematologic	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary, noted in the SmPC, section 4.4: *There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.*and in section 4.8 Undesirable effects – Post-marketing experience with saquinavir
Hepatobiliary-hepatotoxicity	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary, noted in the SmPC, section 4.8 Undesirable effects – Post-marketing experience with saquinavir

Increase in psychiatric disorders	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; noted in the SmPC in Table 2 –common psychiatric disorders seen in MaxCmin2 study (≥ 1 % and < 10 %) were decreased libido and sleep disorder.
Risk of hypersensitivity-allergic reactions	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; noted in the SmPC in Table 2 –common immune system disorders seen in MaxCmin2 study (≥ 1 % and < 10 %) was hypersensitivity and also included in the post-marketing section.
HIV associated malignancies: Kaposis sarcoma, NHL	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary.
Development of wasting syndrome	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary, noted in the SmPC, sections 4.4 and 4.8: *Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8). Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump).*
Risk of opportunistic infections including Esophageal candidiasis, Pneumocystis carinii, CMV retinitis, M. avium	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary, noted in the SmPC, Warnings and Precautions: *Patients should be informed that saquinavir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should also be advised that they might experience undesirable effects associated with co-administered medications.*
Important Missing Information		
Limited clinical data in	Close observation through	No particular risk minimization activity is considered necessary; the SmPC,

patients with renal impairment	routine pharmacovigilance system.	section 4.4, contains a corresponding warning: *Renal clearance is only a minor elimination pathway, the principal route of metabolism and excretion for saquinavir being via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing saquinavir/ritonavir in this population.*
Limited clinical data in children less than 16 years of age	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; there is insufficient information to recommend a saquinavir dose. Recent analysis for pediatric studies could provide dosing information in ages 2 to 16 years of age but currently is not available. The SmPC, section 4.4, contains a corresponding warning: *The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.*
Limited clinical data in adults over 60 years of age	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; there is insufficient information to recommend a saquinavir dose. Recent analysis for pediatric studies could provide dosing information in ages 2 to 16 years of age but currently is not available. The SmPC, section 4.4, contains a corresponding warning: *The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.*
Limited safety data on patient's ability to drive and use machines	Close observation through routine pharmacovigilance system.	No particular risk minimization activity is considered necessary; the SmPC; section 4.7, contains the following information: *Invirase may have a minor influence on the ability to drive and use machines. Dizziness and fatigue have been reported during treatment with Invirase. No studies on the effects on the ability to drive and use machines have been performed.*
Sub-populations with Genetic Polymorphism for Long QT Syndrome	Contraindication in labeling for congenital or documented acquired QT prolongation	Labeling Restrictions, patient and family history and baseline ECG abnormalities
Patients with cardiac impairment and baseline ECG abnormalities	Contraindication in labeling for patients with clinically relevant heart failure with reduced left-ventricular	Labeling Restrictions, patient history and baseline ECG abnormalities

	ejection fraction, previous history of symptomatic arrhythmias, clinically relevant bradycardia	