CLINICAL REVIEW of SUBMISSION (b) (4)

NDAs:	NDA 20628/S-34 (capsule) and 21785/S-11 (tablet)
Drug and Indication:	Invirase® (saquinavir) for the treatment of HIV-1 infection in combination with other antiretroviral agents and ritonavir
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Marketed Formulation:	200 mg hard capsule or 500 mg film coated tablet
Applicant:	Hoffman La-Roche, Inc.
Date submitted:	July 29, 2012
Reviewer Name:	Charu Mullick, MD
Date of review:	November 15, 2012

1. Recommendations/Risk Benefit Assessment

a. Recommendation on Regulatory Action

(b) (4) pediatric doses which are both safe from the perspective of QT/PR prolongation and efficacious could not be determined, (b) (4).

(b) (4) the Applicant is required to include pediatric clinical trial information in the Invirase Package Insert as these studies were submitted in response to a Written Request issued under the Best Pharmaceuticals for Children Act (BPCA). Through submission of data and study reports from pediatric clinical trials, the sponsor has fulfilled postmarketing requirements linked to the Pediatric Research Equity Act (PREA).

b. Risk Benefit Assessment

Saquinavir dosed 50 mg/kg twice daily with ritonavir, in combination with other antiretroviral agents, (b) (4) NV20911 and (b) (4) HIVNAT-017. significant prolongations of corrected QT interval and PR interval were observed at these SQV exposures in the adult thorough QT (TQT) study. Although no QT/PR prolongation events were observed in pediatric trials, these trials were small and did not include routine electrocardiogram (ECG) monitoring and therefore were not adequate to identify this safety concern. QT prolongation, particularly QT intervals greater than 500 msec, is associated with torsades de points, a potentially life-threatening polymorphic ventricular tachycardia. PR prolongation can also result in cardiac conduction abnormalities. (b) (4)

(b) (4)

Currently, 18 ARV agents are approved for use in the pediatric population. These include six agents (lopinavir/ritonavir, atazanavir, darunavir, fosamprenavir, ritonavir, and tipranavir) in the protease inhibitor class, the same mechanistic class as saquinavir. (b) (4)

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2. Introduction and Regulatory Background

a. Product Information

Saquinavir has been marketed in the United States since initial approval in 1995. At present, only Invirase tablets (500 mg strength) and capsules (200 mg strength) are marketed. The recommended Invirase dose is 1000 mg with 100 mg ritonavir taken twice daily for patients 16 years and older. No pediatric formulation of Invirase has been developed.

b. Regulatory Background

(b) (4) . The pediatric studies in the supplement were submitted in response to two postmarketing requirements issued under the PREA:

- NDA 20628 PMR # 1972-1: Deferred pediatric studies under PREA for the treatment of HIV infection in combination with other antiretroviral agents in pediatric patients ages 4 months to adolescence.

- NDA 21785 PMR # 643-1: Deferred pediatric studies under PREA for the treatment of HIV infection in combination with other antiretroviral agents in pediatric patients ages 4 months to adolescence.

The supplement included safety, pharmacokinetic (PK), and antiviral activity data from two key pediatric clinical trials, NV20911 and HIVNAT-017. Study NV20911 enrolled subjects 2 months to 6 years of age, and study HIVNAT-017 enrolled subjects 6 years to 16 years of age. The clinical study report from a third pediatric trial PACTG 397 provided additional supportive safety in subjects ages 3 to 16 years. No new or a pediatric-specific formulation was proposed with the supplemental NDA. Pediatric dosing was based on administration of intact medication or dispersal of contents of broken capsule in jam, baby formula, or sugar syrup for subjects unable to swallow intact medication.

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c. Currently Available Treatments (b) (4)

In the pediatric population, 18 antiretroviral medications from six classes are approved to treat HIV infection (Table 1). In the protease inhibitor (PI) class, several agents including lopinavir/ritonavir, atazanavir, darunavir, fosamprenavir, and ritonavir (rtv) are approved for use.

Table 1: Currently approved pediatric antiretroviral drugs

Drug Class	Generic Name	Trade Name
Nucleoside reverse transcriptase inhibitor (NRTI)	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
PI	Ritonavir (rtv)	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir (LPVR/rtv)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®
	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RALT)	Isentress®
Fusion Inhibitor	Enfuvirtide (T-20)	Fuzeon®

3. Significant Issues Related to Other Review Disciplines

There are no new issues for Chemistry Manufacturing and Controls (CMC), clinical virology, or pharmacology-toxicology disciplines.

Clinical Pharmacology

(b) (4)

his section summarizes pertinent clinical pharmacology/ pharmacometrics findings. Please refer to pharmacometrics review by Dr. Jeffry Florian for details.

Pediatric exposure-response relationship

In study NV20911, mean saquinavir exposures with the (b) (4) dosing exceeded exposures in HIV-infected adults (historical mean exposures). Pediatric exposures were about 35-194% higher in AUC0-12h and 56-320% higher in Cmax values relative to mean values in HIV-infected adults. (b) (4)

The pediatric exposure-response relationship was generally similar to adult exposure-response.

SQV exposure-response relationship for QT/PR prolongation

In the adult TQT study, a dose-response relationship was observed for QT and PR prolongation at the studied therapeutic and supratherapeutic doses. A concentration relationship was identified for PR prolongation, but not for QTc prolongation. For interpretation of QT/PR prolongation with adult vs. (b) (4) pediatric exposures, the following Table 2 was prepared to display comparative exposures for (b) (4) pediatric dosing, the adult HIV-infected therapeutic dose, and therapeutic and supratherapeutic doses administered in the TQT study (further modified by me to include mean QTc prolongation in SQV TQT study). (b) (4) pediatric doses SQV exposures are expected to fall in the range of exposures achieved with therapeutic and supratherapeutic dose in the TQT study, doses which resulted in QTc prolongation of 18.9 and 30.2 msec, respectively. Please refer to Section 6 Pediatric Safety Assessment, under Risk for QT and PR prolongation at (b) (4) pediatric dose, for the relevant clinical discussion.

Table 2: Saquinavir PK parameters in Adults and (b) (4) Pediatric Dosing and QT prolongation observed in the TQT study

Population	Regimen, SQV/RTV (mg, b.i.d.)	SQV AUC, ug.hr/mL (SD) [CI]		SQV Cmax, ug/mL (SD) [CI]		Maximum change in QTcF on Day 3 (upper bound 95% CI), ms
		Day 3	Steady State	Day 3	Steady State	
Healthy volunteers (NP21562)	1000/100	-	36.6 (9.7)	-	6.1 (1.5)	-
Healthy volunteers (NP21249)	1000/100	94.8 (30.6)	-	11.2 (3.3)	-	18.9 (22) ms
Healthy volunteers (NP21562)	1500/100	-	42.7 (20.9)	-	6.8 (3.1)	-
Healthy volunteers (NP21249)	1500/100	141.0 (44.3)	-	15.9 (4.4)	-	30.2 (33) ms
HIV-1 Infected Adults (Label)	1000/100	*37.8-48.2**	14.6 [10.2-20.9]	*5.6**	*2.4**	Cannot predict+
HIV-1 Infected Adults (Literature)	1000/100	*32.9-91.5**	12.7-27.7	*3.5-9.1**	1.9-3.9	Cannot predict+
HIV-1 Infected Pediatrics 2 to <6 years (NV20911)	50 mg/kg, 3 mg/kg (body weight 5-<15 kg) or 2.5 mg/kg (body weight >15 kg [max 100 mg])	*96.6-123.2**	37.3 [10.6-65.3]	*11.2-14.3**	6.1 [1.6-10.3]	Cannot predict+

*Predicted exposures based on ratio of day 3 to steady state exposures in healthy volunteers and the ratio of exposures between healthy volunteers and HIV-1 infected adults (at steady state).

+ Cannot accurately predict QT prolongation at steady state as a concentration-QT relationship for the entire SQV time course could not be determined from the TQT study

Source: Compiled from Clinical Pharmacology and Pharmacometrics review by Dr. Jeffry Florian NDAs 21785/S-034 and 20628/S-011 and QT-IRT review of the TQT study NP21249 by Dr. Hao Zhu NDAs 21785/20628.

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4. Sources of Clinical Data and Review Strategy

(b) (4)

My review summarizes outcomes of the Applicant's methods validation assay and PK modeling, and focuses on pediatric safety assessment from the perspective of QT/PR prolongation. No data analysis was performed. Please refer to the Clinical Review for the original pediatric sNDA by Dr. Tafadzwa Vargas-Kasambira for efficacy and safety analysis of data from the SQV pediatric trials.

A brief description of the two pivotal pediatric trials which formed the principal source of clinical data is provided. Study NV20911 was a 48-week, open-label, single-arm trial evaluating safety, PK, and antiviral activity of SQV in subjects aged 4 months to 6 years. The SQV dose was 50 mg/kg BID plus ritonavir oral solution administered with at least two background ARVs. The trial enrolled 18 pediatric subjects at sites in Argentina, Spain and Thailand. Study HIVNAT-017 was a 96-week, open-label, single-arm trial evaluating safety, PK and antiviral activity of SQV in pediatric subjects aged 4 years to 15 years. Saquinavir was dosed at 50 mg/kg BID administered with LPV/rtv. A total of 50 subjects were enrolled at two sites in Thailand.

5. Summary of Efficacy

As mentioned previously, no antiviral activity data are included in this submission. Pediatric efficacy analyses were performed by Dr. Vargas-Kasambira during review of the supplemental NDA. Key efficacy findings from his review are summarized here: In the HIVNAT-017 trial, virologic response defined as proportion of subjects achieving HIV viral load (VL) < 400 copies/ml was observed in 78% of subjects at Week 96. HIV VL < 50 copies/ml was observed in 66% of these subjects. In the NV20911 trial, 72% of subjects achieved VL < 400 copies/ml and 61% had VL < 50 copies/ml at Week 48.

In both trials, SQV was dosed 50 mg/kg BID up to a maximum 1000 mg BID, the adult recommended dose. (b) (4)

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6. Assessment of Safety

New safety issues for use of SQV in the pediatric population were not identified in Dr. Vargas-Kasambira's review of data from trials NV20911 and HIVNAT-017. Commonly reported treatment-related adverse events in these trials were diarrhea, vomiting, and abdominal pain.

Saquinavir causes prolongation of the QT interval and PR interval in adults. In SQV pediatric trials, no cases of QT/PR prolongation or related cardiac adverse events were observed. However, these trials had small sample size (enrolled between 18 to 50 subjects) and ECGs were not obtained as part of routine safety assessments. (b) (4)

Background for Safety Concern for QT and PR Prolongation

SQV Thorough QT study findings

Saquinavir can cause QT and PR prolongation based on positive findings in TQT study NP21249. In this study, healthy volunteer subjects were randomized to 1000 mg/100 mg SQV/rtv (therapeutic dose), 1500 mg/100 mg SQV/rtv (supratherapeutic dose), moxifloxacin control, or placebo. In healthy subjects, SQV AUC and Cmax are twice the AUC and Cmax achieved in HIV-infected subjects. ECG monitoring was performed at Day 3 of dosing to coincide with maximal SQV exposures. The maximum mean increase in QTc interval from placebo and with baseline correction was 18.9 msec and 30.2 msec at therapeutic and supratherapeutic dose, respectively. Increases in QTcF were dose-dependent. The concentration-response relationship was not linear as increases in QTcF were observed 12 hours post-dose, at a time when SQV plasma concentrations had declined. The reason for continued effects on QT interval despite decreasing plasma drug concentration is not known. The effects of cumulative dosing on QT prolongation are also not known as ECGs were not obtained after Day 3 in the TQT study. Importantly, lack of a linear concentration-response relationship limits the ability to predict the magnitude of QT prolongation at higher or lower SQV concentrations or at steady state.

The maximum mean change in PR interval from placebo and after baseline correction was 28.6 msec and 38.4 msec at therapeutic and supratherapeutic dose, respectively. PR prolongation was dose-dependent as well as exposure-dependent. Absolute PR interval exceeding 200 msec, the clinical cut-off for abnormal PR prolongation or first degree AV block, was observed in 40% and 47% of subjects at therapeutic and supratherapeutic dose, respectively. For details of the TQT study and analysis of results, please refer to the QT-IRT review by Hao Zhu dated June 9, 2010.

Postmarketing cases

Review of the FDA Adverse Event Reporting System (AERS) database by Office of Surveillance and Epidemiology (OSE) identified five cases of QT prolongation, one case of torsades de pointes, and seven cases of atrioventricular conduction block. These

cases were confounded by concomitant use of medications associated with QT or PR prolongation or insufficient information.

Based on the positive QT study, the Invirase label carries a warning for QT and PR prolongation and recommends ECG monitoring prior to initiating treatment. Further contraindications were included for medical conditions predisposing to or concomitant use of drugs known to cause QT/PR prolongation. For details, please refer to OSE review by Paula Gish dated January 8, 2010 and clinical review of the safety labeling change by Dr. Vargas-Kasambira dated October 5, 2010.

Pediatric Safety in the Context of QT/PR prolongation

The Applicant's safety assessment and risk-benefit analysis (b) (4) does not specifically discuss risk of QT/PR prolongation (b) (4) Below is my safety assessment for (b) (4) in the context of concerns for QT/PR prolongation and an overall risk-benefit analysis for pediatric dosing. Note that no safety data were included in this submission.

A) Risk for QT and PR prolongation at (b) (4) pediatric dose

(b) (4) pediatric dosing yields SQV exposures which exceed exposures achieved with dosing HIV-infected adults. Exposures (b) (4) are expected to fall in the exposure range where mean QTc prolongation of 18.9 and 30.2 msec was observed in the TQT study (at therapeutic and supratherapeutic dose respectively). It is generally accepted that drugs prolonging QTc interval by 5 to 20 msec may be associated with proarrhythmic risk, and drugs with effect size exceeding 20 msec have substantially higher proarrhythmic risk [1]. (b) (4) .

The risk of clinical events due to prolonged QT/PR interval are expected to be highest in the first week of starting SQV, the time when highest SQV concentrations will occur. However, the extent of QT/PR prolongation at steady state concentrations is not known because ECGs were not obtained after day 3 in the TQT study. Because delayed effects on QTc prolongation were observed in the TQT study, it is possible that QT prolongation greater than that observed in the TQT study may occur.

Based on available pediatric clinical experience, the QTc prolongation risk in the pediatric population is considered to be similar to adults (refer to the QT-IRT memorandum by Dr. Suchitra Balakrishnan dated December 22, 2010). Although no QT/PR prolongation was observed (b) (4) in pediatric trials, these trials were not of adequate size or designed to assess these events. An additional consideration is PK variability in children, as patients who achieve higher than anticipated drug exposures will be at greater risk for QT prolongation. Saquinavir exposure, and consequently risk for QT prolongation, is highest during the first week of dosing but available pediatric PK data was determined at drug steady state (i.e., 10-14 days) further confounding estimates of risk in pediatric patients. Similarly, PR

[1] Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

prolongation is a concern at higher pediatric exposures which are in the range or exceed those observed in the adult TQT study.

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[redacted] (b) (4)

7. Labeling Recommendations

The review team's conclusion [redacted] (b) (4) was conveyed to the Applicant on November 9, 2011. This communication also notified them about the BPCA requirement for labeling pediatric trial description and findings. The Applicant requested modeling simulation analysis supporting FDA conclusions, and subsequently agreed with FDA's proposed language with few modifications. Key recommendations from the review team are outlined here. Exact wording of the labeling remains under negotiation at this time.

- **Highlights section**: **Use in Specific Population**
  Pediatric Use: Pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined (8.4)

- **FPI sections 1 and 2 Indication and Usage, Dosage and Administration**: [redacted] (b) (4)

- **Section 6 Adverse Drug Reactions**: Applicant's proposed language describing safety in pediatric trials NV20911 and HIVNAT-017 in section 6.2 Adverse Drug Reactions in Clinical Trials was accepted with minor revision.

- **Section 8.4 Pediatric Use**: [redacted] (b) (4) FDA proposed new language to provide description of the pivotal pediatric trials [redacted] (b) (4) The Applicant accepted FDA's proposal with modifications highlighted below:

  > Steady state saquinavir exposures observed in pediatric trials were substantially higher than historical data in adults where dose- and exposure-dependent QTc and PR prolongation [redacted] (b) (4) [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.2, 12.3)*]. Although [redacted] (b) (4) were not reported in these pediatric trials, the trials were small and not designed to evaluate QT or PR intervals. Modeling and simulation assessment of pharmacokinetic/pharmacodynamic relationships in pediatric subjects suggest that reducing the INVIRASE dose to minimize risk of QT prolongation is likely reduce antiviral efficacy. In addition, no clinical efficacy data are available at a lower Invirase dose in pediatric subjects. Therefore, pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined.

- **Section 12.3 Pharmacokinetics**: Applicant's proposed language for PK findings from NV20911 was accepted. The reason for not including PK from HIVNAT-017 is provided in this section.

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/s/

CHARU J MULLICK
11/30/2012

LINDA L LEWIS
11/30/2012
I concur with Dr. Mullick's assessment.