Health Canada Endorsed Important Safety Information on INVIRASE® (saquinavir mesylate)

April 14, 2010

Dear Health Care Professional

Subject: Association of INVIRASE® (saquinavir mesylate) with significant dose-dependent prolongations of QT and PR intervals in healthy volunteers

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform healthcare professionals of important new safety information regarding the use of INVIRASE® (saquinavir mesylate) and significant dose-dependent prolongations of QT and PR intervals in healthy volunteers.

INVIRASE is authorized for the treatment of HIV-1 infected adult patients. INVIRASE should only be given in combination with ritonavir and other antiretroviral medicinal products.

Based on the findings of a dedicated electrocardiogram study with INVIRASE/ritonavir in healthy volunteers:

- Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted INVIRASE.
- INVIRASE/ritonavir should not be used in patients already taking medications known to cause QT interval prolongation or in patients with a history of QT interval prolongation
- Caution is warranted when administering ritonavir-boosted INVIRASE to patients with pre-existing conduction system disease

As a consequence of the findings of a dedicated electrocardiogram study with INVIRASE/ritonavir in healthy volunteers, the Canadian Product Monograph (CPM) has been updated. The updated CPM can be at found at: http://www.rochecanada.com or can be accessed by performing a search in Health Canada's Drug Product Database at: http://www.hc-sc.gc.ca/dhp-

mps/prodpharma/databasdon/index-eng.php. The updates to the product monograph include the following information:

In a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) study in healthy male and female volunteers aged 18 to 55 years old (N=59) PR interval prolongation of > 200 msec (1^{st} degree AV-block) was observed in 40% of subjects receiving a therapeutic dose of INVIRASE/ritonavir (1000/100 mg bid) and 47% of subjects receiving a supratherapeutic dose of INVIRASE/ritonavir (1500/100 mg bid) on Day 3 compared with 3 % of subjects in the active control (moxifloxacin) arm and 5% in the placebo group. 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 bid and 1500/100 mg bid, respectively, while the PR-intervals remained relatively unchanged in the placebo and moxifloxacin arms.

Maximum mean QT prolongations (QTcS; study-specific QT interval correction) of 18.9 msec, 30.2 msec. and 12.2 msec were observed in the 1000/100 mg, 1500/100 mg, and moxifloxacin (positive control) groups, respectively. The majority of subjects (89% and 80% in the therapeutic dose and supra-therapeutic dose groups, respectively) had a QTcS of < 450 msec and none had a QTc interval of > 500 msec.

Ritonavir-boosted INVIRASE should not be used in patients already taking medications known to cause QT interval prolongation, such as Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic drugs, or in patients with a history of QT interval prolongation. Caution should be taken when administering ritonavir-boosted INVIRASE with any medication which can significantly increase either the QT or PR interval. Caution is also warranted when administering ritonavir-boosted INVIRASE to patients with a known history of QT prolongation or medical conditions predisposing to QT prolongation (e.g. electrolyte disturbances) and/or patients with pre-existing conduction system disease (e.g. first-degree AV block or second- or third degree AV block).

Roche continues to monitor adverse events of QT and PR interval prolongation associated with INVIRASE and ritonavir-boosted INVIRASE and is committed to providing you with the most current information for our products.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious prolongations of QT and PR intervals or other serious or unexpected adverse reactions in patients receiving INVIRASE should be reported to Hoffmann-La Roche Limited or Health Canada at the following addresses:

Hoffmann-La Roche Limited
Drug Safety Department
2455 Meadowpine Boulevard
Mississauga, Ontario, L5N 6L7
Or call toll free at: 1-888-762-4388
Or fax at: 905-542-5864
Or email to: Mississauga.drug_safety@roche.com

Any suspected adverse reaction can also be reported to:
Canada Vigilance Program
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701D
Ottawa, Ontario, K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
CanadaVigilance@hc-sc.gc.ca

To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789

Postage paid labels, the Canada Vigilance Reporting Forms and the Adverse Reaction Reporting Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section. The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

To change your mailing address or fax number, contact the Market Authorization Holder.

Should you have any questions or require additional information regarding the use of INVIRASE, please contact the Drug Information Department at Hoffmann-La Roche Limited at 1-888-762-4388 from 8:30 a.m. to 4:30 p.m. Monday to Friday Eastern Standard Time.

Sincerely,

Lorenzo Biondi,
Vice President, Medical and Regulatory Affairs
Hoffmann-La Roche Limited