CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-628/S-016

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Division of Antiviral Drug Products

REGULATORY PROJECT MANAGER (CONSUMER SAFETY OFFICER) REVIEW: SUPPLEMENTAL LABEL REVISION

Application Number: NDA 20-628/SLR-016

Name of Drug: INVIRASE® (saquinavir mesylate) Capsules

Sponsor: Hoffman-La Roche, Inc
340 Kingsland Street
Nutley, NJ 07110-1199

Material Reviewed:

Submission Dates:	February 1, 2001	Supplemental Application: Labeling (SLR)
	March 28, 2001	Supplemental Application: Labeling (SLR)
	April 27, 2001	Supplemental Application: Labeling (SLR)
Receipt Dates:	February 1, 2001	Supplemental Application: Labeling (SLR)
	March 29, 2001	Supplemental Application: Labeling (SLR)
	April 30, 2001	Supplemental Application: Labeling (SLR)

Background and Summary

This labeling supplement was submitted in response to letters from the Division about needed revisions to the INVIRASE® labeling. The labeling supplement was compared both manually and electronically to the final printed labeling approved November 14, 2000. The SLR addresses the following issues:

1. Implementation of a risk communication strategy designed to alert patients of the need to find out about potential drug interactions with INVIRASE®. This strategy includes:

   A. Use of the ALERT message on the container (bottle) labeling (INVIRASE® is not distributed with a carton.)

   B. Inclusion of the ALERT message in the professional package insert in the "WARNINGS" section and in the "PRECAUTIONS: Information for Patients" section. (INVIRASE® is not distributed with a Patient Package Insert.)

2. Inclusion of statements in the professional package insert regarding the interaction of INVIRASE® with St. John's Wort in the "WARNINGS" section and the "PRECAUTIONS: Information for Patients" section. (INVIRASE® is not distributed with a Patient Package Insert.)

REVISIONS TO THE LABEL: The sponsor proposes the following changes:

1. ALERT Message added to the INVIRASE® Bottle Label

   Page 20 of attached labeling:

   ALERT
   Find out about medicines that should not be taken with INVIRASE.

2. Inclusion of the ALERT message in the professional package insert in the "WARNINGS" section:

   Page 9, Lines 276 - 277 The following statement was added to the "WARNINGS" section as the first paragraph.

   "**ALERT: Find out about medicines that should not be taken with INVIRASE.** This statement is included on the product's bottle label."

3. Inclusion of the ALERT message in the professional package insert in the "PRECAUTIONS: *Information for Patients*" section:

   Page 11, Lines 345 - 347: The following statement was added to the "PRECAUTIONS" section immediately following the section entitled "*Resistance/Cross-resistance*" (Line 260.)

   "A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with INVIRASE."**

4. Inclusion of statements in the professional package insert regarding the interaction of INVIRASE® with St. John's Wort in the "WARNINGS" section:
   Page 10, Lines 296 - 300: The following statement was added to the "WARNINGS" section as the last paragraph immediately before the "PRECAUTIONS: *General*" section:

"Concomitant use of INVIRASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including INVIRASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of INVIRASE and lead to loss of virologic response and possible resistance to INVIRASE or to the class of protease inhibitors."

5. Inclusion of statements in the professional package insert regarding the interaction of INVIRASE® with St. John's Wort in the "PRECAUTIONS: *Information for Patients*" section:

   Page 11, Lines 349 - 351: The following statement was added to the "PRECAUTIONS: *Information for Patients*" section as the second paragraph:

   "INVIRASE may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication, or herbal products, particularly St. John's wort."

Conclusions

All of the changes noted in the labeling review were acceptable. An approval letter will be sent and the sponsor will be asked to submit a final printed labeling identical to the draft labeling submitted April 27, 2001 for the INVIRASE container (bottle) label and the package insert.

Marsha S. Holloman, BS Pharm, JD — Date
Regulatory Health Project Manager

Anthony W. DeCicco, RPh — Date
Chief, Project Management Staff

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marsha Holloman
6/19/02 03:21:45 PM
CSO

Tony DeCicco
6/24/02 04:49:58 PM
CSO

Appears This Way
On Original

MED WATCH	A.1. Patient Identifier	O.9. MFr. /
	GN	19981.

B.5. Describe event or problem

[continuation:] information:
The center is conducting a prospective study on the incidence and drug etiology of severe skin diseases. Diagnosis of a Stevens-Johnson-Syndrome has been made by an expert panel, labelled as "possible". Drug causality was assessed by the experts using an algorithm. As for Lasix (furosemide) causality was assessed "well possible"; for other concomitantly given drugs causality was assessed with:

"well possible" - lamotrigine, cefuroxime sodium, cefuroximaxetile
"possible" - netilmicine sulphate, ipratropium bromide, salbutamol sulphate, acetylcysteine, oxymetazoline hydrochloride
"conditional" - vigabatrin, propranolol hydrochloride, dexamethasone, simethicone, colecalciferol/ sodium fluoride
"unrelated" - gentamicin sulphate
'unlikely" - lactulose, potassium chloride, glucose, sodium chloride, Paediafusin II (glucose/glyceroldihydrogenphosphate di-sodium/ potassium/ sodium/calcium/ magnesium chloride/sodium acetate/L-malic acid
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Epicrisis:
This report involves a 2-year-old female child with a medical history of state after severe perinatal asphyxia, periventricular leucomalacia, microcephalia, agenesia of corpus callosum, dysmorphism syndrome of unknown origin, epilepsy, severe mental disability, atrioseptal defect (stage II), arterial hypertension, edema, hypopotassemia, constipation, meteorism, suspicion of pneumonia, suspicion of sepsis, infection of the upper respiratory tract, mucolysis, caries and conjunctivitis.

Up to 17-FEB-1998 the child had been hospitalised due to dyspnoe syndrome with acute infection of the upper respiratory tract and suspicion of pneumonia and sepsis.
From 10/FEB/98 - 03/03/98 the child was treated with furosemide solution (3x0.5 mg/day/po) for treatment of edema.
In addition, several other drugs had been given.
On 25-FEB-98 first signs of Stevens-Johnson-Syndrome, palmoplantar and perianal maculae, appeared, followed on 01-MAR-98 by vesicles on the oral and genital mucous membrane, erosions on the anal mucous membrane and conjunctivitis.
On 03-03-98 the child was transferred to hospital with fever up to 38.5 *C and erosions of the lips.
The event was still ongoing on 11-MAR-98; the outcome is unknown.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) STEVENS-JOHNSON-SYNDROME	YES	UNK	UNK	YES	possibly associated with concomitant drug(s)
(Sx) MACULAE PALMAR, PLANTAR AND PERIANAL					
(Sx) VESICLES ON ORAL AND GENITAL MUCOUS MEMBRANE					
(Sx) EROSIONS MUCOUS MEMBRANE (LIPS, ANAL)					
(Sx) FEVER (38.5 *C)					
(Sx) CONJUNCTIVITIS					

MED WATCH	A.1. Patient identifier	G.9. Mfr. report number	Page 7 of 8
	GN	199812498HPD	

Individual Safety Report

3123199-6-00-07

B.5. Describe event or problem

[continuation:]

B.7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] EPILEPSY
ARTERIAL HYPERTENSION
EPILEPSY
CONSTIPATION
METEORISM
CARIES/PROPHYLAXIS OF RACHITIS
HYPOPOTASSEMIA
PARENTERAL FEEDING
PARENTERAL FEEDING
CONJUNCTIVITIS

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

02/10/1998 to 03/03/1998 Duration: 3 weeks 1 day

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #2)

02/04/1998 to 03/01/1998 Duration: 3 weeks 5 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #3)

02/11/1998 to 02/15/1998 Duration: 5 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #4)

02/11/1998 to 02/15/1998 Duration: 5 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #5)

02/11/1998 to 02/15/1998 Duration: 5 days

C.4. Diagnosis for use (indication) (Suspect #5)

INFECTION OF UPPER RESPIRATORY TRACT

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #6)

02/11/1998 to 02/15/1998 Duration: 5 days

C.4. Diagnosis for use (indication) (Suspect #6)

INFECTION OF UPPER RESPIRATORY TRACT

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #7)

02/11/1998 to 02/17/1998 Duration: 6 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #8)

02/12/1998 to 02/17/1998 Duration: 6 days

C.4. Diagnosis for use (indication) (Suspect #8)

INFECTION OF UPPER RESPIRATORY TRACT

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #9)

02/16/1998 to 02/20/1998 Duration: 5 days

AUG 31 1998

MED WATCH	A.1. Patient identifier	G.9. Mfr. report number	Page 8 of 8
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C.10. **Concomitant medical products** and therapy dates (exclude treatment of event)

[continuation:] LEFAX
D-FLUORETTEN
POTASSIUM CHLORIDE
GLUCOSE
PAEDIAFUSIN
SODIUM CHLORIDE
REFOBACIN

Individual Safety Report
3123199-6-00-08

AUG 21 1998

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