DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20685/S-075

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Kristin Rittenhouse
Manager, World Regulatory Affairs
P.O. Box 1000, UG2C-50,
North Wales, PA 19454-1099

Dear Ms. Rittenhouse:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Crixivan® (indinavir sulfate) Capsules.

We acknowledge receipt of your amendments dated January 6, 2012 in response to our General Advice letter dated, December 12, 2011.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

This supplemental new drug application provides for revisions to the labeling for Crixivan® (indinavir sulfate) Capsules, consistent with our October 19 and December 12, 2011 letters, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The Table 7 in the **CONTRAINDICATIONS** section has been revised as follows:

Table 7
Drug Interactions With Crixivan: Contraindicated Drugs

Drug Class	**Drugs Within Class That Are Contraindicated With CRIXIVAN**
Alpha 1-adrenoreceptor antagonist	alfuzosin

Antiarrhythmics	amiodarone
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	cisapride
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Neuroleptics	pimozide
PDE5 Inhibitors	Revatio[1] (sildenafil) [for treatment of pulmonary arterial hypertension]
Sedative/hypnotics	oral midazolam, triazolam, alprazolam

[1] Registered trademark of Pfizer, Inc.

2. The first paragraph under the "**WARNINGS**/Drug Interactions" which references coadministration with the statins has been revised as follows:

   Concomitant use of CRIXIVAN with lovastatin~~,~~ **or** simvastatin is contraindicated due to increased risk of myopathy including rhabdomyolysis.~~, or rosuvastatin is not recommended.~~ Caution should be exercised if CRIXIVAN is used concurrently with atorvastatin or rosuvastatin. Titrate the atorvastatin and rosuvastatin doses carefully and use the lowest necessary dose with CRIXIVAN~~HIV protease inhibitors, including CRIXIVAN, are used concurrently with atorvastatin. The interaction of CRIXIVAN with pravastatin and fluvastatin is not known. The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including CRIXIVAN, are used in combination with these statin drugs~~ (see PRECAUTIONS, *Drug Interactions*).

3. The **PRECAUTIONS/ Immune Reconstitution Syndrome** sub-section has been revised as follows:

   Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including CRIXIVAN. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

   Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. A paragraph begins with "CRIXIVAN is not a cure for HIV**…..**" in the **PRECAUTIONS/**Information for Patients sub-section has been revised as follows: CRIXIVAN is not a cure for HIV-1 infection and patients may continue to ~~develop~~ experience ~~opportunistic infections and other complications~~ illnesses associated with HIV-1 ~~disease~~ infection, including opportunistic infections. Patients should remain under the care of a physician when using CRIXIVAN. ~~The long-term effects of CRIXIVAN are unknown at~~

~~this time. CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.~~

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if CRIXIVAN can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

5. The Table 8 and 9, in the **PRECAUTIONS/Drug Interactions** sub-section, were revised as follows:

Table 8 **Drugs That Should Not Be Coadministered With CRIXIVAN**	
Drug Class: Drug Name	**Clinical Comment**
HMG-CoA Reductase inhibitors: lovastatin, simvastatin	CONTRAINDICATED due to an increased risk for serious reactions such as myopathy including rhabdomyolysis.
~~HMG-CoA Reductase inhibitors: lovastatin, simvastatin, rosuvastatin~~	(b) (4) ~~Potential for serious reactions such as risk of myopathy including rhabdomyolysis.~~

Table 9 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See also CLINICAL PHARMACOLOGY for magnitude of interaction, WARNINGS and DOSAGE AND ADMINISTRATION.)		
Drug Name	*Effect*	Clinical Comment
HMG-CoA Reductase Inhibitors: atorvastatin, rosuvastatin ~~pravastatin, fluvastatin~~	↑ atorvastatin concentration ↑ rosuvastatin concentration ~~pravastatin, fluvastatininteraction not studied~~	The atorvastatin and rosuvastatin doses should be carefully titrated; ~~U~~use the lowest ~~possible~~ dose necessary ~~of atorvastatin~~ with careful monitoring~~.~~ ~~D~~during treatment with CRIXIVAN. ~~If no alternative treatment is available, use with careful monitoring.~~

5. **Patient Prescribing Information**:

a. The "**Does CRIXIVAN cure HIV or AIDS?**" section has been revised as follows:
~~CRIXIVAN is not a cure for HIV or AIDS. People taking CRIXIVAN may still develop infections or other conditions associated with HIV. Because of this, it is very important for you to remain under the care of a doctor. Although CRIXIVAN is not a cure for HIV or AIDS, CRIXIVAN can help reduce your chances of getting illnesses, including death, associated with HIV. CRIXIVAN may not have these effects in all patients.~~ CRIXIVAN does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using CRIXIVAN.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.

b. The "**Does CRIXIVAN reduce the risk of passing HIV to others?**" section has been deleted.

c. "**What other medical problems or conditions should I discuss with my doctor?**"/the second bulleted paragraph in "Talk to your doctor if:" sub-section has been revised as follows:

- You are breast-feeding. ~~You should stop breast-feeding if you are taking CRIXIVAN~~. **Do not breastfeed.** We do not know if CRIXIVAN can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

d. The **MEDICINES YOU SHOULD NOT TAKE WITH CRIXIVAN** section has been revised as follows:

Oral VERSED® (midazolam)	HALCION® (triazolam)
ORAP® (pimozide)	XANAX® (alprazolam)
PROPULSID® (cisapride)	REVATIO®(sildenafil for the treatment of pulmonary arterial Hypertension)
CORDARONE® (amiodarone)	UROXATRAL® (alfuzosin)
HISMANAL® (astemizole)	Ergot medications (e.g., Wigraine®, Cafergot®, D.H.E. 45®, Migranal®, Ergotrate®, and Methergine®)
	ZOCOR® (simvastatin)
	MEVACOR® (lovastatin)

Taking CRIXIVAN with the above medications could result in serious or life-threatening problems (such as irregular heartbeat or excessive sleepiness).

In addition, you should not take CRIXIVAN with the following:

Rifampin, known as RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE®.

~~It is not recommended to take CRIXIVAN with the cholesterol-lowering drugs MEVACOR® (lovastatin), ZOCOR® (simvastatin), or CRESTOR® (rosuvastatin) because of possible drug interactions.~~ There is also an increased risk of drug interactions between CRIXIVAN and LIPITOR® (atorvastatin) and CRESTOR® (rosuvastatin); talk to your doctor before you take any of these cholesterol-reducing drugs with CRIXIVAN.

e. The editorial revision has been made in the MEDICINES YOU CAN TAKE WITH CRIXIVAN section as follows to include top two medicines listed within table grid as follows:

MEDICINES YOU CAN TAKE WITH CRIXIVAN

~~RETROVIR®~~
~~(zidovudine, ZDV~~
~~also called AZT)~~

~~EPIVIR™~~
~~(lamivudine, 3TC)~~

RETROVIR® (zidovudine, ZDV also called AZT)	EPIVIR™ (lamivudine, 3TC)
ZERIT® (stavudine, d4T)	isoniazid (INH)

6. The revision date has been changed from November 2010 to Month Year at the end of the package insert and the patient information labeling.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

KENDALL A MARCUS
02/17/2012