PUBLIC ASSESSMENT REPORT

Nevirapine Tablets 200 mg

International Nonproprietary Name (INN): **Nevirapine**

Abstract

Nevirapine Tablets 200 mg, supplied by Zhejiang Huahai Pharmaceuticals Co., Ltd., Xunqiao, Linhai, Zhejiang 317024, China, was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Nevirapine Tablets 200 mg are safe and effective for use as recommended in the submitted labeling. The USFDA was unable to grant final approval to this ANDA at the time of review due to existing patent protection. Therefore, the ANDA was **tentatively approved** on July 10, 2007. This determination was based upon information available to the agency at that time (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product).

On the basis of USFDA **tentative approval**, Nevirapine Tablets 200 mg were placed with the footnote "USFDA" on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (WHO Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification Programme list with the note "USFDA" are added to the list based on scientific assessment and inspections conducted by the USFDA. Product listing as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of the product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

Nevirapine is indicated for the treatment of HIV infection in combination with other antiretroviral agents. Detailed conditions for the use of the product are described in the Summary of Product Characteristics (SPC) and Scientific Discussion, Parts 4 and 6 of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Nevirapine Tablets 200 mg is the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine. The API is a well-established and documented product for the treatment of HIV/AIDS in combination with other products.

Nevirapine has been investigated in several clinical trials in both treatment-naïve and treatment-experienced patients. These studies have demonstrated a significant increase in CD4 T-lymphocyte counts and a decrease in HIV viral load. The most frequently reported adverse events related to nevirapine therapy are rash, nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. The most serious safety problems with nevirapine include Stevens-

Johnson syndrome, toxic epidermal necrolysis, hepatitis/hepatic failure, and hypersensitivity reactions characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

The risk/benefit profile of nevirapine demonstrated an acceptable safety profile and adequate antiretroviral activity.

All Accepted Presentations

Status	USFDA Tentative Approval
INN	Nevirapine
Strength	200 mg
Form	Tablets
Route of administration	Oral
Packaging	Bottle
Package size	Sixty (60) tablets

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nevirapine Tablets 200 mg

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or health care provider or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. WHAT NEVIRAPINE TABLETS ARE AND WHAT THEY ARE USED FOR

Nevirapine belongs to a group of antiviral medicines (also known as antiretrovirals) called non-nucleoside reverse transcriptase inhibitors (NNRTIs). These medicines are used to treat Human Immunodeficiency Virus (HIV) infection. You must take nevirapine with other anti-HIV medicines. When taken with other anti-HIV medicines, nevirapine can reduce the amount of HIV virus in your body and increase the number of CD4 cells, a type of white blood cell that play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Nevirapine Tablets varies between patients. Your doctor or health care provider will monitor the effectiveness of your treatment.

Nevirapine may improve your condition but is not a cure for HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with Nevirapine Tablets has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

During your treatment, other infections linked to your weakened immunity (called “opportunistic infections”) may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE NEVIRAPINE TABLETS

Do not take Nevirapine Tablets if:

- You are allergic (hypersensitive) to nevirapine or any of the other ingredients of Nevirapine (see section 6, “What Nevirapine Tablets Contain”).
- You previously experienced hepatitis, severe skin rash, or liver injury while on nevirapine treatment.

- You have ever experiencd serious liver or skin reactions that happened when you took nevirapine.
- You take certain other medicines (see "Taking Other Medicines" below).

Take special care with Nevirapine Tablets
Before using this medicine, tell your doctor or health care provider if you suffer from or have ever suffered from kidney or liver disease.

The first 18 weeks of treatment with Nevirapine Tablets is an important period for close surveillance for the occurrence of severe and life threatening skin reactions and serious liver injuries. During this period the dosage of Nevirapine Tablets prescribed by your doctor or health care provider must be strictly adhered to, especially during the first 14 days of treatment, the "lead-in" period (see section 3, "How to take Nevirapine Tablets").

Skin reactions
Nevirapine can result in skin reactions and hypersensitivity reactions, which in the worst cases can be serious and life-threatening and which have resulted in fatalities (see section 4, "Possible Side Effects"). Hypersensitivity (allergic) reactions can occur in the form of rash accompanied by other side effects such as fever, blistering, mouth sores, eye inflammation, facial swelling, general swelling, muscle or joint aches, a reduction in white blood cells (granulocytopenia), general feelings of illness or severe problems with liver or kidneys.

If you have any rash symptoms, please inform your doctor or health care provider immediately, who will advise you whether you should stop taking Nevirapine Tablets.

If you experience a severe rash or any rash associated with other side effects of a hypersensitivity reaction, you must stop taking Nevirapine Tablets and contact your doctor or health care provider immediately. Such reactions can be potentially life-threatening.

Liver injuries
Nevirapine can result in liver toxicity, which in the worst cases can be serious and life-threatening and has resulted in fatalities. Patients with reduced liver function and patients with either hepatitis B or C infection are at increased risk for severe and potentially fatal liver damage while taking antiretroviral therapy in general, including Nevirapine Tablets. Adult females and patients with higher CD4 cell counts at the start of treatment with Nevirapine Tablets have an increased risk of developing liver problems.

Unless the benefit outweighs the risk, Nevirapine Tablets should not be started in women with CD4 cell counts greater than 250 cells/mm3 or in men with CD4 cell counts greater than 400 cells/mm3.

If you experience symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting, or jaundice (yellow discoloration of the skin and eyes), you should discontinue taking Nevirapine Tablets and contact your doctor or health care provider immediately.

If you develop severe liver, skin, or hypersensitivity reactions during treatment with Nevirapine Tablets, you must **NOT TAKE** Nevirapine Tablets again before you speak with your doctor or health care practitioner. **DO NOT** restart Nevirapine Tablets unless you are directed to do so by your doctor or health care practitioner.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present but had no obvious symptoms. If you notice any symptoms of infection, please inform your doctor or health care provider immediately.

A change in distribution, accumulation, or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor or health care provider if you notice changes in body fat.

You must take Nevirapine Tablets every day. This medicine helps to control your condition but is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines
Please tell your doctor, health care provider, or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription ("over the counter" medicines). These may affect the action of Nevirapine Tablets, or Nevirapine Tablets may affect their action.

Do not combine Nevirapine Tablets with ketoconazole, as nevirapine decreases ketoconazole levels in the body and therefore reduces ketoconazole's medicinal activity.

Rifampicin (rifampin) should not be taken with Nevirapine Tablets.

Nevirapine may decrease methadone levels in blood which can lead to withdrawal symptoms. Tell your doctor or health care provider if you take methadone, so they can adjust your methadone dosing schedule.

Nevirapine decreases the effect of oral contraceptives. Do *not* use oral contraceptives when you take Nevirapine Tablets. Use an alternate contraceptive method such as barrier contraception (For example, condoms or a diaphragm).

Do not take St. John's Wort or herbal preparations containing St. John's Wort when you are taking Nevirapine Tablets. St. John's Wort may reduce the efficacy of nevirapine.

Taking Nevirapine with food and drink
Nevirapine Tablets may be taken with or without food.

Pregnancy
If you become pregnant, or are planning to become pregnant, talk to your doctor or health care provider to discuss potential benefits and adverse effects of your antiretroviral therapy to you and your child.

If you have taken Nevirapine Tablets during your pregnancy, your doctor or health care provider may request regular clinic visits to monitor the development of your child. Such visits may include blood tests and other tests.

Breastfeeding
Since nevirapine and the HIV virus pass into breast milk it is recommended that HIV infected woman taking nevirapine do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Driving and using machines
No information on the effects of nevirapine on the ability to drive and use machines is available.

3. HOW TO TAKE NEVIRAPINE TABLETS

Always take Nevirapine Tablets exactly as your doctor or health care provider instructs you. Ask your doctor, health care provider, or pharmacist if you are not sure.

The usual Nevirapine Tablet dosage is one 200 mg tablet *once daily* for the first 14 days of treatment. This "lead in" period has been shown to lower the incidence of skin rash. As of the third week of treatment (starting with day #15 of treatment) the dosage is one 200 mg tablet *twice daily*.

Nevirapine may be taken with or without food.

If you stop taking Nevirapine Tablets for more than 7 (seven) days your doctor will instruct you to re-start the 14-day "lead in" period (described above) before returning to the regular twice daily dose.

Nevirapine will always be taken in combination with other antiretroviral medication. Always read and follow all instructions within the supplied package leaflets of all medicines you are prescribed.

If you take more Nevirapine than you should
If you take too many Nevirapine Tablets, or if someone accidentally swallows some of your Nevirapine Tablets, there is no immediate danger. However, you should contact your doctor, health care provider, or the nearest hospital emergency department for further advice.

If you forget to take Nevirapine Tablets
If you accidentally miss a dose then simply take your normal dose when the next one is due. Do not take a double dose to make up for a missed or forgotten dose.

If you stop taking Nevirapine Tablets
If you stop taking Nevirapine Tablets for any reason (other than a forgotten dose), you must contact your doctor or health care provider. If you stop taking Nevirapine Tablets for more than 7 (seven) days your doctor will instruct you to start the 14-day "lead in" period again before returning to the twice daily dose.

If you have any further questions on the use of Nevirapine Tablets, ask your doctor, health care provider, or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nevirapine Tablets can cause side effects, although not everybody experiences them. When treating HIV infection, it is not always possible to tell the difference between unwanted effects caused by nevirapine, or those caused by any other medicines you may

be taking at the same time, or by HIV disease. For this reason, it is important that you tell your doctor or health care provider of any change in your health.

Short-term mild adverse reactions to combination antiretroviral therapy are common. After you start taking Nevirapine Tablets, the following side effects may occur: rash, headache, nausea and vomiting, abdominal pain or cramps, diarrhea, fatigue, malaise, fever, and muscle aches. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

The most serious adverse reactions are severe and potentially life threatening skin reactions (known as Stevens-Johnson syndrome and toxic epidermal necrolysis), hepatitis, liver failure, and hypersensitivity (allergic) reactions. These serious adverse reactions are characterized by rash with constitutional symptoms such as fever, joint pain, muscle aches, increased size of lymph nodes, plus visceral (organ) involvement such as inflammation of the liver, hepatitis, an increase in eosinophils (a variety of white blood cells involved in the immune system), decreased overall number of white blood cells, and kidney dysfunction. The first 18 weeks of treatment is a critical period and requires close monitoring. Most cases of severe rash occur in the first 6 weeks of treatment.

Commonly reported (greater than 1 in every 100 patients treated) side effects are: rash, allergic reactions, muscle pain, headache, nausea, liver function test abnormalities, and hepatitis.

The following side effects are uncommon (between 1 in 100 and 1 in 1,000 patients treated): abdominal pain, jaundice, Steven-Johnson syndrome, hives, fatigue, and fever.

There are rare reports (between 1 in 1000 to 1 in 10,000 patients treated) of decreased white and red blood cells, severe allergic reaction characterized by rash, facial swelling, spasm of airways in the lungs, or shock (called hypersensitivity and anaphylaxis), diarrhea, liver failure and sudden or very rapid onset of hepatitis, toxic epidermal necrolysis, and swelling of the skin (angioedema).

The major side effects of Nevirapine Tablets are severe and life threatening skin reactions and serious liver injuries. These reactions occur mainly in the first 18 weeks of treatment with nevirapine. This is therefore an important period which requires close surveillance.

Combination antiretroviral therapy may cause a condition called lactic acidosis, which is a build-up of lactic acid in the body that can cause dehydration and coma. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting, and stomach pain, may indicate the development of lactic acidosis.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These changes can include loss of fat from the legs, arms, and face, increased abdominal (belly) fat, breast enlargement, and fatty lumps on the back of the neck (“buffalo hump”). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipemia (increased fats in the blood), and resistance to insulin.

If you experience any side effects described in this leaflet, tell your doctor or health care provider immediately. If you notice any side effects or possible side effects *not* listed in this leaflet, you should also advise your doctor or health care provider. If you are not sure if you are experiencing side effects while taking Nevirapine Tablets, ask your doctor, health care provider, or pharmacist.

5. HOW TO STORE NEVIRAPINE TABLETS

Store at room temperature between 15º-30ºC (59º-86ºF). Store out of the sight and reach of children, in a dry place protected from light.

Do not use Nevirapine Tablets after the expiration (expiry) date which is printed on the label and on the carton. The expiration date refers to the last day of the month cited.

Do not use Nevirapine Tablets if there is any sign that the packaging has been opened or tampered with, or if you notice any visible signs of deterioration such as fading in color or discoloration of any of the tablets, or if any of the tablets are brittle or break easily.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. Proper disposal of medicine will help protect the environment.

6. FURTHER INFORMATION

What Nevirapine Tablets contain

- The active ingredient is nevirapine.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, and magnesium stearate.

What Nevirapine tablets 200 mg look like and contents of the pack

Nevirapine Tablets 200 mg are white to off-white oval shaped tablets, debossed on one side with "H9050" with a single bisect line on the other side, packaged in bottles of 60 tablets.

For further information about this product, contact the supplier: Zhejiang Huahai Pharmaceutical Co., Ltd., Xunqiao, Linhai, Zhejiang 317024, China.

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nevirapine Tablets 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of Nevirapine
For excipients see 6.1

3. PHARMACEUTICAL FORM

White to off-white oval-shaped tablet debossed with "H9050" on one side and a single bisect line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevirapine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

Nevirapine Tablets 200 mg are for oral use.

Nevirapine should be prescribed by a physician or other professional health care provider experienced in the management of HIV-1 infection.

Patients 16 years and older:
200 mg once daily for the first 14 days followed by one 200 mg tablet twice daily.

*Pediatric patients 2 month to 16 years**
(The dosing directions below are not applicable for fixed dose preparations).
4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg daily for any patient.
*Children should be assessed for the ability to swallow tablets. If unable to do so, an oral solution formulation should be prescribed.

The lead-in period allows for induction of drug-metabolizing hepatic enzymes and has been found to lessen the frequency of rash.

Nevirapine may be taken with or without food.

Liver Disease
Nevirapine should not be used in patients with severe liver disease (Child-Pugh Classification Score >7) or pre-treatment liver enzymes > 5 times the upper limit of normal (ULN).

Renal Impairment
In subjects with end-stage renal disease requiring hemodialysis an additional 200 mg dose of nevirapine following each hemodialysis treatment should be given to offset the effects of dialysis on nevirapine clearance. Patients with creatinine clearance ≥ 20 ml/min do not require an adjustment in nevirapine dosing.

4.3 Contraindications

Nevirapine is contraindicated in patients with clinically significant hypersensitivity to nevirapine or to any of the components contained in the formulation.

Nevirapine is contraindicated in patients with severe hepatic impairment (Child-Pugh Classification Score > 7).

Nevirapine must ***not*** be re-administered to patients who have required permanent discontinuation for severe rash, hypersensitivity reactions, or liver toxicity due to nevirapine.

Nevirapine should ***not*** be used for post-exposure prophylaxis in HIV-1 negative individuals.

4.4 Special warnings and special precautions for use

The USFDA issued a public health advisory on April 30, 2009, informing health care providers and patients about recent safety-related changes to the Viramune® (nevirapine) label (package insert) and about appropriate use of HIV triple combination therapy containing nevirapine. That Advisory is included below. The Viramune® (nevirapine) label has been revised several times over the last two years to include more information on liver toxicity associated with long term nevirapine use. It is now recommended against starting nevirapine treatment in women with CD4+cell counts greater than 250 cells/mm3 unless benefits clearly outweigh risks. This recommendation is based on a higher observed risk of serious liver toxicity in patients with higher CD4 cell counts prior to initiation of therapy.

USFDA Public Health Advisory for Nevirapine
Both symptomatic and asymptomatic liver toxicity are observed with long term use of nevirapine in combination with other HIV drugs. Asymptomatic liver toxicity is defined as increases in liver enzymes without associated clinical signs or symptoms and is similar to that seen with other antiretroviral drugs. Symptomatic liver toxicity is more common with nevirapine compared to other antiretroviral drugs. Important information regarding symptomatic nevirapine liver toxicity is summarized below:

- Symptomatic nevirapine liver toxicity consists of elevated liver enzymes plus at least one symptom, which is typically rash but may include flu-like symptoms or fever. The severity of symptomatic liver toxicity ranges from mild symptoms with liver enzyme abnormalities to rapidly occurring liver failure and death.
- Symptomatic nevirapine liver toxicity typically occurs after only a few weeks of dosing and may progress to liver failure despite monitoring of laboratory tests, which is not characteristic of other antiretrovirals.
- Females and patients with higher CD4+ cell counts are at increased risk of liver toxicity. Females have a three-fold higher risk of symptomatic nevirapine liver toxicity than

males, and females with CD4+ cell counts > 250 cells/mm3 have a 12 fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts < 250 (11% vs. 0.9%). Males with CD4+ cell counts > 400 cells/mm3 have a five-fold higher risk of symptomatic liver toxicity than males with CD4+ cell counts < 400 (6.3% vs. 1.2%).

- Nevirapine-related deaths due to symptomatic liver toxicity, including some in HIV-infected pregnant women, have been reported. Serious and fatal liver toxicity has not been reported after single doses of nevirapine.

In spite of the potential for serious and life-threatening liver toxicity and skin rashes with nevirapine, there are multiple reasons why nevirapine remains an important part of an HIV treatment regimen for many HIV-infected individuals world-wide. These reasons include:

- Triple antiretroviral regimens have been shown to have a large impact on the reduction of AIDS morbidity and mortality. Triple antiretroviral drug regimens containing a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as nevirapine, are standard of care for HIV treatment and are needed to adequately and durably suppress virus.
- Many options are needed for HIV-infected patients since resistance to antiretroviral drugs or to an entire antiretroviral class can develop.
- Symptomatic liver toxicity has not been reported with the use of single doses of nevirapine to the mother and to the child for prevention of perinatal HIV infection.
- Alternatives to nevirapine are limited by other toxicities, potential drug interactions, and by the risk of drug related birth defects if given to a female in the first trimester of pregnancy.
- Nevirapine liver toxicity is less frequent (<2% for both males and females with CD4+ cell counts <250 cells/mm3) when started in patients with lower CD4 counts. Therefore, symptomatic liver toxicity in resource poor countries is likely to be much lower if World Health Organization standards are used for starting treatment. The WHO recommends the initiation of ART treatment in patients with advanced disease or with CD4 counts < 200 cells/mm3.
- Nevirapine is chemically stable in environmental conditions where other antiretrovirals are not.
- Symptomatic liver toxicity has not been reported in HIV-infected children, and nevirapine is available in a liquid formulation while many other antiretrovirals are not.

The seriousness of the underlying disease must be considered as part of the risk benefit analysis when treating HIV-infected patients. HIV infection will progress to AIDS and death if untreated. Treatment with combination antiretroviral drugs, including nevirapine, can slow clinical progression and may delay the development of AIDS or death for years. Health care providers should weigh the benefits and risks associated with nevirapine use before prescribing nevirapine for the treatment of their HIV-infected patients.

Skin reactions

Rash is a common adverse reaction to nevirapine. Cases are typically mild to moderate but severe and life-threatening skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. These have occurred most commonly during the initial 6 weeks of therapy, but may occur up to 18 weeks after initiating nevirapine. (In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.) Patients should be advised to report symptoms of a hypersensitivity reaction immediately (e.g. fever, rash, arthralgias or myalgias). Nevirapine

must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by systemic symptoms.

Prednisone or antihistamine (cetrizine) does *not* decrease the incidence of nevirapine-associated rash.

Factors associated with nevirapine-associated rash are higher baseline CD4 count, higher baseline HIV RNA level, female sex, higher age, and higher nevirapine concentration. Once daily dosing (400 mg) is associated with a higher rate of rash than twice daily dosing (200 mg BID).

Patients with rash should be assessed for liver toxicity.

Nevirapine must *not* be restarted following severe skin reactions.

If fever or other features of hypersensitivity develop during the 200 mg QD dose-induction period, the dose should *not* be increased to 200 mg BID (twice daily) at 14 days unless *all features of hypersensitivity have resolved*. Patients should be advised that recurrence of these symptoms is likely at the increased dose.

Liver disease
Severe and life-threatening liver toxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. This has mainly occurred during the initial 6 weeks of therapy but may occur up to 18 weeks after initiating nevirapine. Symptoms are a hypersensitivity reaction that may be accompanied by rash, eosinophilia, and systemic symptoms (fever, rash, arthralgias or myalgias). Factors associated with nevirapine-associated liver toxicity are female sex, higher baseline CD4 counts, higher baseline levels of alanine aminotransferase, hepatitis C co-infection and alcohol abuse. Women with CD4 cell counts >250 cells/mm3 had a 12-fold higher risk of symptomatic liver toxicity compared to women with CD4 counts <250 cells/mm^3. A 5-fold increased risk was observed in men with CD4 counts > 400 cells/mm^3.

Monitoring of liver transaminases should be performed if the patient experiences signs or symptoms (e.g. anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness) suggestive of liver toxicity.

Hepatic laboratory abnormalities are more frequent with once daily dosing (400 mg QD) than with twice daily dosing (200 mg BID).

Patients developing signs or symptoms of liver toxicity and/or hypersensitivity should seek prompt medical evaluation. Nevirapine must be permanently discontinued in any patient experiencing severe liver toxicity.

Discontinuation and reintroduction of nevirapine
Because nevirapine is an inducer of drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than two weeks and is to be restarted later, nevirapine should be reintroduced with a dose escalation period of 200 mg once daily for 14 days, followed by a 200 mg twice-daily regimen.

Resistance
Single-dose use of nevirapine leads to a high rate of nevirapine resistance. Nevirapine must not be used as a single agent to treat HIV or added to a failing regimen.

As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

Post-exposure prophylaxis (PEP)
Serious liver toxicity, including liver failure requiring transplantation, has been reported in uninfected individuals receiving nevirapine in the setting of PEP. Nevirapine should ***not*** be used for post-exposure prophylaxis in HIV-1 negative individuals.

4.5 Interaction with other medicinal products and other forms of interaction

Nevirapine is a mild to moderate inducer of the hepatic enzyme CYP3A. It is therefore possible that co-administration of nevirapine with protease inhibitors may result in alterations in the plasma concentration of either agent.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. Additional clinical monitoring is warranted when coadministering these drugs.

The *in vitro* interaction between nevirapine and warfarin is complex. When giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is coadministered with nevirapine, anticoagulation levels must be monitored frequently.

Nevirapine decreases plasma concentrations of methadone. Methadone-maintained patients beginning nevirapine therapy should be assessed for evidence of withdrawal and methadone dose should be adjusted accordingly.

Ketoconazole levels are reduced > 60% and is therefore not recommended to be used with nevirapine.

Rifampicin may significantly decrease levels of nevirapine. These two agents should not be used concomitantly.

Exposure to nevirapine can be reduced by concomitant use of the herb St. John's Wort (*Hypericum perforatum*). St. John’s Wort or herbal preparations containing St John’s Wort must not be combined with nevirapine.

See Section 4 (“Summary of Product Safety and Efficacy; Drug Interactions, related side effects and contraindications”) of the Scientific Discussion, Part 6 of this Public Assessment Report, for an extensive discussion of drug interactions with nevirapine.

4.6 Pregnancy and lactation

Pregnancy: Nevirapine is assigned FDA Pregnancy Category C status (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).

Nursing Mothers: Nevirapine crosses the placenta and is found in breast milk of lactating mothers. Because of the potential for postnatal HIV transmission and adverse effects caused by nevirapine in nursing infants, HIV-infected mothers should be instructed not to breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects of nevirapine on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse events have been reported in controlled clinical trials and case series.

The adverse events considered at least possibly related to treatment with nevirapine are listed below by body system, organ class, and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Blood and lymphatic systems disorders
Common: Neutropenia

Immune system disorders
Common: Allergic reactions
Rare: Hypersensitivity syndrome

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Nausea

Hepatobiliary disorders
Common: Liver transaminase abnormalities
Uncommon: Jaundice
Rare: Liver failure

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Stevens-Johnson syndrome
Rare: Toxic epidermal necrolysis

General disorders
Uncommon: Fatigue and fever

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases, and weight decrease. All of these effects subsided following discontinuation of nevirapine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: non-nucleoside reverse transcriptase inhibitor (NNRTI), antiretroviral, ATC code: J05AG01

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Clinical Efficacy
Nevirapine has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with other nucleoside analogue(s) and/or a Protease Inhibitor. In recent studies by intention-to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/ml after 48 weeks of combination antiretroviral treatment.

HIV-1 resistance to nevirapine involves the development of mutations in the reverse transcriptase gene at positions 100, 103, 106, 108, 181, 188 and 190 (www.iasusa.org). The K103N or Y188L mutation alone prevents clinical utility of nevirapine. The V106M mutation is more common in HIV-1 subtype C than subtype B and confers cross-resistance to nevirapine and efavirenz.

Rapid emergence of resistance to NNRTIs, including nevirapine, is likely to occur in cases of virological failure.

Patients who are infected with known nevirapine-resistant HIV or patients who have previously experienced virological failure on a nevirapine- or efavirenz-containing regimen may not respond to further treatment with a combination regimen containing nevirapine or efavirenz.

Perinatal Transmission
Nevirapine, given to pregnant mothers in labor who have not received standard combination antiretroviral therapy during pregnancy, prevents vertical transmission of HIV-1 infection. A single dose of 200 mg of nevirapine given at the onset of labor to the mother and 2 mg/kg given to the infant within 72 hours of birth is highly effective in reducing mother-to-child transmission

of HIV-1. No benefit was demonstrated in administering additional nevirapine in the intra-partum (newborn) period in cases where women received prenatal care and antenatal ART, and elective caesarean section was made available.

Single-dose use of nevirapine leads to a high rate of nevirapine resistance.

5.2 Pharmacokinetics

Absorption and Bioavailability: Nevirapine is rapidly absorbed following oral administration. Bioavailability is > 90%. Peak plasma concentrations of 2.0 mg/ml occur within 4 hours after dosing. At a therapeutic dose of 200 mg twice daily, mean steady-state Cmax and Cmin of nevirapine in plasma were 5.7 mg/ml and 3.7 mg/ml, respectively. The area under the curve (AUC) is 109 μg.h/ml.

Distribution: The estimated volume of distribution is 1.2 L/kg. The observed half-life is 25 to 30 hours following multiple dosing. Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Nevirapine readily crosses the placenta and is also found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 μg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% ± 5% of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism and Elimination: Nevirapine is actively biotransformed primarily via cytochrome P450 isozyme CYP3A. Cytochrome P450 metabolism, glucuronide conjugation and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine elimination in humans. Less than 5% is excreted through the kidneys.

5.3 Preclinical Safety Data

Preclinical data revealed no special hazard for humans other than those observed based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, evidence of impaired fertility was seen in rats. In carcinogenicity studies, nevirapine induced hepatic tumors in rats and mice. In rats these findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action. The mechanism of tumors in mice is not yet clarified and therefore their relevance in humans is yet to be determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 25ºC (77ºF) with occasional excusions permitted between 15º-30ºC (59º-86ºF).

6.5 Nature and contents of container

White to off-white oval shaped tablets debossed with “H9050” on one side and bisected on the other side, packaged in bottles of 60 tablets each with a child resistant cap.

6.6 Instructions for use and handling and disposal

No special requirements.

7. SUPPLIER

Zhejiang Huahai Pharmaceutical Co., Ltd., Xunqiao, Linhai, Zhejiang 317024, China

8. DATE OF USFDA TENTATIVE APPROVAL

July 10, 2007

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Nevirapine Tablets 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Nevirapine Tablets 200 mg

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains 200 mg of nevirapine

3. LIST OF EXCIPIENTS

Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, magnesium stearate

4. PHARMACEUTICAL FORM AND CONTENTS

White to off-white oval shaped tablets debossed with “H9050” on one side and bisected on the other side, packaged in bottles of 60 tablets each with a child resistant cap.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION DATE

<EXP MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Store at 25ºC (77ºF) with occasional excusions permitted between 15º-30ºC (59º-86ºF)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Zhejiang Huahai Pharmaceutical Co., Ltd., Xunqiao, Linhai, Zhejiang 317024, China

12. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

13. INSTRUCTIONS FOR USE

SCIENTIFIC DISCUSSION

DISCUSSION

Name of the Finished Pharmaceutical Product	Nevirapine
Supplier	Zhejiang Huahai Pharmaceutical Co., Ltd., Xunqiao, Linhai, Zhejiang 317024, China
Active Pharmaceutical Ingredient(s) (API)	Nevirapine
International Non-proprietary Name	Nevirapine
Pharmaco-therapeutic group (ATC Code)	J05A G01
Therapeutic indication	Nevirapine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

Nevirapine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Nevirapine is not indicated for use in patients with clinically significant hypersensitivity to nevirapine or to any of the components contained in the formulation.

It is recommended that therapy be initiated only on the advice of a physician experienced in clinical management of HIV/AIDS.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA), and was reviewed under the President's Emergency Plan for Aids Relief (PEPFAR).

Composition
Nevirapine Tablets 200 mg are presented as white to off-white oval shaped tablets debossed with "H9050" on one side and bisected on the other side. Each tablet contains 200 mg of nevirapine. Other inactive ingredients include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, and magnesium stearate.

Control of Active Pharmaceutical Ingredient (API)
Nevirapine controls are consistent with cGMP and USP requirements and take into account product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are in line with the requirements of major internationally used pharmacopoeias and guidelines for tablets. The test methods have been adequately validated.

Stability
Stability studies have been conducted and results show that the products conform with the proposed end of shelf life specification including description, disintegration time, dissolution, assay, and degradation products. The stability protocols adopted by the firm placed the product under accelerated (40° ± 2°C/75 ± 5%RH) and long term (25° ± 2°C/60 ± 5%RH) conditions for stability monitoring. Stability data for this product in the proposed marketing containers conforms to specifications. Based on the stability data provided the proposed expiration dating is acceptable.

Conclusion
The data submitted ensures acceptable quality of the finished medicinal product when stored under the conditions specified on the label.

3. Assessment of Bioequivalence

Both fasted and fed bioequivalent studies (two-way, crossover) were performed for comparison of Nevirapine Tablets 200 mg vs. Viramune® (nevirapine) Tablets 200 mg (Boehringer Ingelheim Pharmaceuticals, Inc.). The formulations were administered to 30 normal, healthy adults, with 24 completing the study. Nevirapine concentrations in human plasma samples from

the bioequivalent studies were determined using an LC/MS/MS method. Based on the statistical analysis, Nevirapine Tablets 200 mg compared to the reference drug product met the 90% confidence intervals for the mean ratio of the log transformed AUC0-72 and Cmax (0.8000-1.2500) for bioequivalence under fasted and fed conditions in accordance with bioequivalence criteria established by the USFDA Office of Generic Drugs Division of Bioequivalence.

4. Summary of Product Safety and Efficacy

Introduction

Background
Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site.

Product Design
The development strategy for Nevirapine Tablets 200 mg was concentrated on compatibility of the active ingredient nevirapine with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Unique Product Characteristics
Nevirapine Tablets 200 mg are presented as white to off-white oval-shaped tablets debossed with "H9050" on one side and bisected on the other side.

Approved Indication
Nevirapine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics
The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Pharmacokinetics

Pharmacokinetics in Adults

Absorption and Bioavailability: Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 μg/mL (7.5 μM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 μg/ mL (17 ± 7 μM), (n = 242) were attained at 400 mg/day.

Nevirapine has been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When Nevirapine 200 mg was administered to 24 healthy adults (12 female, 12 male), with

either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure (AUCt) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Therefore, Nevirapine may be administered with or without food or antacids.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk.

Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 μg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Pharmacokinetics in Special Populations

Renal/Hepatic Dysfunction: The pharmacokinetics of nevirapine have not been evaluated in patients with either renal or hepatic dysfunction.

Gender: In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (Vdss/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine

oral clearance or plasma concentrations following either single- or multiple-dose administration(s).

Race: An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median Cminss = 4.7 μg/mL Black, 3.8 μg/mL Hispanic, 4.3 μg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Geriatric Patients: Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18–68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

Pediatric Patients: The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. In one study (ACTG 165), nine HIV-1-infected children ranging in age from 9 months to 14 years were administered a single dose (7.5 mg, 30 mg, or 120 mg per m2; n=3 per dose) of nevirapine suspension after an overnight fast. The mean nevirapine apparent clearance adjusted for body weight was greater in children compared to adults.

In a multiple dose study, nevirapine suspension or tablets (240 or 400 mg/m2/day) were administered as monotherapy or in combination with zidovudine or zidovudine + didanosine to 37 HIV-1-infected pediatric patients with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months-15 years). The majority of these patients received 120 mg/m2 daily of nevirapine for approximately 4 weeks followed by 120 mg/m2/twice daily (patients > 9 years of age) or 200 mg/m2 twice daily (patients ≤ 9 years of age). Apparent clearance of nevirapine adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. Apparent clearance of nevirapine adjusted for body weight was at least two-fold greater in children younger than 8 years compared to adults. Pediatric dosing regimens were selected in order to achieve steady-state plasma concentrations in pediatric patients that approximate those in adults.

Evaluation of the pharmacokinetics of nevirapine in neonates is ongoing.

Drug Interactions, related side effects and contraindications

Nucleoside Analogues: No dosage adjustments are required when nevirapine is taken in combination with zidovudine, didanosine, or zalcitabine. Results from studies in HIV-1 infected patients who were administered nevirapine with different combinations of didanosine or zalcitabine, on a background of zidovudine therapy, indicated that no clinically significant pharmacokinetic interactions occurred when the nucleoside analogues were administered in combination with nevirapine.

Non-Nucleoside Reverse Transcriptase Inhibitors: HIV-infected patients who received efavirenz (600 mg/day) for ≥ 2 weeks were given nevirapine (400 mg/day) and pharmacokinetic parameters of both drugs were evaluated after 4 weeks. Nevirapine pharmacokinetics appeared to be unaffected by coadministration with efavirenz compared to historical controls. The AUC of efavirenz, however, was reduced by 22%, the Cmin was reduced by 36%, and the Cmax was reduced by 17%. While the clinical implications of this interaction are not known, because of overlapping resistance and lack of additive antiretroviral effects, nevirapine should not be co-administered with efavirenz or other NNRTIs (e,g., delavirdine, etravirine).

Protease Inhibitors:

- *Ritonavir*: No dosage adjustments are required when nevirapine 200 is taken in combination with ritonavir (based on nevirapine 200 mg once daily for 14 days followed by twice daily for 28 days). Results from a 49-day study in HIV-infected patients (n=14) who received nevirapine and ritonavir (600 mg b.i.d. using a gradual dose escalation regimen) indicated that their coadministration did not affect ritonavir AUC or Cmax. Comparison of nevirapine pharmacokinetics from this study to historical data suggested that coadministration did not affect the pharmacokinetics of nevirapine.
- *Indinavir*: Results from a 36-day study in HIV-infected patients (n=19) administered nevirapine (200 mg once daily for 14 days followed by twice daily for 28 days) and indinavir (800 mg q8h) indicated that their coadministration led to a 28% mean decrease (95% CI -39, -16) in indinavir AUC and an 11% mean decrease (95% CI -49, +59) in indinavir Cmax. The clinical significance of this interaction is not known. Comparison of nevirapine pharmacokinetics from this study to historical data suggested that coadministration did not affect the pharmacokinetics of nevirapine. Some research has suggested increasing the dose of indinavir to 1000 mg every 8 hours when given in combination with nevirapine or to administer a ritonavir "boosted" indinavir dose.
- *Saquinavir*: Results from a 42-day study in HIV-infected patients (n=23) administered nevirapine (200 mg once daily for 14 days followed by twice daily for 28 days) and saquinavir (hard gelatin capsules, 600 mg t.i.d.) indicated that their coadministration led to a 24% mean decrease (95% CI -42, -1) in saquinavir AUC and a 28% mean decrease (95% CI -47, -1) in saquinavir Cmax. The clinical significance of this interaction is not known. Coadministration did not affect the pharmacokinetics of nevirapine.
- *Amprenavir*: Nevirapine has the potential to decrease serum concentrations of amprenavir. Appropriate doses of nevirapine or amprenavir for coadministration have not been determined. The coadministration of nevirapine and fosamprenavir is not recommended unless fosamprenavir is "boosted" with ritonavir. The administration of fosamprenavir alone with nevirapine results in an unacceptable decline of amprenavir concentrations. If fosamprenavir and ritonavir, given as the twice daily dosage regimen, is administered with nevirapine, no dosage adjustments are needed. Once daily fosamprenavir and ritonavir dosage coadministered with nevirapine has not been studied.
- *Atazanavir*: ***Do not coadminister atazanavir and nevirapine***. Coadministration leads to substantially decreased atazanavir conentrations and increased nevirapine concentrations, which could lead to toxicity.

CYP enzyme metabolism and related drug interactions
Nevirapine is a substrate of and inducer of CYP3A and CYP2B6. Maximal induction of CYP3A occurrs within 2-4 weeks of initiating multiple-dose therapy. Since nevirapine is an inducer of CYP3A, decreased plasma concentrations of drugs extensively metabolized by this enzyme should be expected with coadministration (see following list).

Monitoring of nevirapine plasma concentrations in patients who received long-term nevirapine treatment indicate that steady-state nevirapine trough plasma concentrations were elevated in patients who received cimetidine (+21%, n=11) and macrolides (+12%, n=24), both known inhibitors of CYP3A. Steady-state nevirapine trough concentrations were reduced in patients who received rifabutin (-16%, n=19) and rifampin (-37%, n=3), also known inducers of CYP3A. Other compounds that are substrates of CYP3A may have decreased plasma concentrations when co-administered with nevirapine. Therefore, careful monitoring of the therapeutic effectiveness of CYP3A-metabolized drugs is recommended when taken in combination with nevirapine.

Nevirapine interactions with drugs metabolized by Cytochrome P450 enzymes

Alfentanil: Alfentanil is metabolized by CYP3A4. Coadministration with nevirapine should be done with caution. Therapeutic monitoring of alfentanil concentrations is recommended.

Ambrisentan: Although this interaction has not been specifically studied, hepatic enzyme inducers such as nevirapine may affect the metabolism of ambrisentan and may necessitate dosage adjustments of ambrisentan.

Amiodarone: Amiodarone is metabolized by CYP3A4. Coadministration with nevirapine should be done with caution. Therapeutic monitoring of amiodarone concentrations is recommended.

Aripiprazole: Decreased blood levels of aripiprazole are expected when the drug is coadministered with CYP3A4-inducers such as nevirapine. A dosage adjustment of aripiprazole is necessary when these drugs are used concomitantly, and conversely, when nevirapine is discontinued in a patient taking aripiprazole.

Barbiturates: Coadministration of nevirapine with barbiturates including phenobarbital will likely increase nevirapine clearance, thereby decreasing nevirapine plasma concentrations. However, since nevirapine also induces CYP3A enzymes, decreases in anticonvulsant serum concentrations may be noted with the possibility of new seizure activity. The appropriate drug-dose adjustments necessary to ensure optimum levels of both antiretroviral drugs and barbiturates are unknown. If used concomitantly, the patient should be observed for changes in the clinical efficacy and concentrations of the antiretroviral and anticonvulsant regimens.

Benzodiazepines: Nevirapine may induce the metabolism of certain benzodiazepines that are metabolized through the cytochrome P450 system. Patients receiving chlordiazepoxide, alprazolam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, prazepam, quazepam, or triazolam should be monitored closely for loss of clinical effects. Lorazepam, oxazepam, and temazepam may be better alternatives as they are not expected to interact with nevirapine.

Buprenorphine: Inducers of CYP3A4 such as nevirapine may induce the metabolism of buprenorphine, which may lead to opiate withdrawal or inadequate pain control. This interaction is most significant if the enzyme-inducing agent is added after buprenorphine therapy has begun; buprenorphine doses may need to be increased. Conversely, buprenorphine doses may need to be decreased if nevirapine is discontinued.

Bortezomib: Bortezomib is a significant substrate for CYP3A4. Coadministration with nevirapine may decrease the exposure to bortezomib and possibly decrease the efficacy of the drug. Patients receiving bortezomib concurrently with CYP3A4 inducers should be closely monitored for potential loss of efficacy.

Carbamazepine: Complex interactions may occur when carbamazepine is administered to patients receiving treatment for HIV infection. The combination regimens used to treat HIV often include substrates, inducers, and inhibitors of several CYP isoenzymes. If carbamazepine is used in patients being treated for HIV, the patient must be closely monitored for antiviral efficacy and seizure control. Appropriate dose adjustments for carbamazepine or the antiretroviral medications are unknown. Coadministration of carbamazepine with non-nucleoside reverse transcriptase inhibitors results in complex interactions. Coadministration with nevirapine, a CYP3A4 substrate and inducer, may increase nevirapine clearance, and thereby decrease nevirapine plasma concentrations. Coadministration may also induce carbamazepine metabolism, leading to reduced carbamazepine concentrations.

Clarithromycin: Coadministration of nevirapine and clarithromycin results in increased nevirapine concentrations (26%) and decreased clarithromycin concentrations (30%). While the 14-OH-clarithromycin (active metabolite) concentrations are increased, this metabolite has reduced activity against Mycobacterium avium-intracellulare complex, and overall activity against this pathogen may be altered. It is not clear if clarithromycin activity against other organisms would be reduced, but reduced efficacy is possible. Alternatives to clarithromycin, such as azithromycin, should be considered in patients who are

taking nevirapine.

Cyclosporine: Nevirapine may induce cyclosporine metabolism, thereby increasing the clearance of cyclosporine. If nevirapine is added to an existing cyclosporine regimen, monitor cyclosporine concentrations closely to avoid loss of clinical efficacy until a new steady-state concentration is achieved. Conversely, if nevirapine is discontinued, cyclosporine concentrations could increase.

Doxercalciferol: Although these interactions have not been specifically studied, hepatic enzyme inducers such as nevirapine may affect the 25-hydroxylation of doxercalciferol and may necessitate dosage adjustments of doxercalciferol. Patients should be monitored for changes in efficacy if these drugs are coadministered.

Ethosuximide: Concurrent administration of nevirapine may result in decreased ethosuximide concentrations due to enzyme induction. Monitor patients closely during concurrent therapy.

Fentanyl: Fentanyl is a substrate of CYP3A4; nevirapine is an inducer of CYP3A4. Coadministration may induce fentanyl metabolism. Induction of fentanyl metabolism may take several days, leading to decreased efficacy and the necessity of an upward dose adjustment.

Gefitinib: CYP3A4 inducers such as nevirapine will decrease the plasma concentrations of gefitinib. In patients receiving potent inducers of CYP3A4, a dosage increase to gefitinib 500 mg/day should be considered in the absence of severe adverse reactions, and the clinical response should be carefully monitored.

HMG-CoA reductase inhibitors (statins): Significant CYP3A4 inducers, such as nevirapine, may decrease the efficacy of HMG-CoA reductase inhibitors (statins) which are CYP3A4 substrates (atorvastatin, cerivastatin, lovastatin, simvastatin). Monitor for potential reduced cholesterol-lowering efficacy when these drugs are coadministered with HMG-CoA reductase inhibitors.

Hormonal contraceptives: Estrogens and progestins are both susceptible to drug interactions with hepatic enzyme inducing drugs. Estrogens are metabolized by CYP3A4. Nevirapine may decrease plasma concentrations of oral or non-oral combination contraceptives. ***Oral or other hormonal contraceptives should not be used as a method of birth control in females taking nevirapine***. If used for hormone replacement therapy, monitor patients for a decrease in clinical effects. Patients should report breakthrough bleeding to their prescriber. Dosage adjustments may be necessary.

Imatinib: Imatinib is metabolized by CYP3A4; nevirapine induces CYP3A4. Use caution if these drugs are coadministered. Decreased imatinib concentrations should be expected with concurrent use.

Interferons: The concomitant use of interferons and non-nucleoside reverse transcriptase inhibitors (NNRTIs) should be done with caution as both can cause hepatic damage. NNRTIs may cause liver damage in the context of hypersensitivity reactions or by direct toxic effects. Chronic HCV infection enhances the risk of developing liver enzyme elevations in patients receiving nevirapine. Closely monitor patients for treatment-associated toxicities, especially hepatic decompensation.

Ketoconazole: Ketoconazole is a substrate and potent inhibitor of the CYP3A4 isoenzyme. Ketoconazole significantly inhibited the formation of nevirapine hydroxylated metabolites, therefore, ketoconazole and nevirapine should not be coadministered. Ketoconazole AUC and Cmax decreased by a median 63% (95% CI -95, +33) and 40% (95% CI -52, +11), respectively, in HIV-infected patients (n=22) who were given nevirapine 200 mg once daily for two weeks followed by 200 mg twice daily for two weeks along with ketoconazole 400 mg daily. Comparison of the pharmacokinetics from this study to historical data suggested that coadministration with ketoconazole may result in a 15-30% increase in nevirapine plasma concentrations. The clinical significance of this observation is not known.

Lidocaine: CYP3A4 is partially responsible for the metabolism of lidocaine; nevirapine induces CYP3A4. Although studies involving nevirapine and lidocaine have not been conducted, coadminister these drugs cautiously, as an upward dosage adjustment of lidocaine may be needed.

Methadone: Nevirapine induces methadone metabolism via CYP3A4 and is associated with significant decreases in methadone concentrations. Methadone AUC decreases by 46% after 3 weeks of starting nevirapine. Patients stabilized on methadone-maintenance therapy may experience narcotic withdrawal symptoms within 7 days of starting nevirapine. Methadone-maintained patients should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly. In one series of patients, an average 45% increase in the methadone dose was required to prevent withdrawal symptoms in patients also receiving nevirapine.

Nilotinib: Nilotinib is an inhibitor while nevirapine is an inducer of CYP3A4. Both are substrates. Coadministration may lead to altered concentrations of either drug. If decreased nilotinib concentrations result, an increased dose may be needed, necessitating careful monitoring for nilotinib-related toxicity. If increased nevirapine concentrations result, related adverse reactions may occur. Carefully monitor patients receiving these drugs together.

Paclitaxel: Coadministration of paclitaxel and nevirapine may lead to decreased paclitaxel concentrations. If these drugs are coadministered, the patient must be carefully monitored for paclitaxel efficacy.

Paricalcitol: If paricalcitol is coadministered with nevirapine, serum concentrations of paricalcitol may be reduced, and dosage adjustments may be required. Monitor plasma iPTH and serum calcium and phosphorous concentrations when these drugs are initiated or discontinued.

Phenytoin: Mechanisms of drug interactions with phenytoin are potentially complex. In general, phenytoin is an inducer of the hepatic cytochrome P450 microsomal enzymes including CYP3A4, CYP2C9, and CYP2C19 isoenzymes. However, a patient's susceptibility to enzyme-induction interactions may be influenced by factors such as age, cigarette smoking, or the presence of liver disease. Phenytoin is metabolized primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce phenytoin's metabolism. If phenytoin is used in patients being treated for HIV, the patient must be closely monitored for antiviral efficacy and seizure control. Appropriate dose adjustments for phenytoin or the antiretroviral medications are unknown. Coadministration with nevirapine may lead to increased phenytoin clearance, thereby decreasing phenytoin plasma concentrations. A similar interaction may occur with the hydantoin anticonvulsant ethotoin, although data are lacking.

Prednisone: The active metabolite of prednisone, prednisolone, is a substrate of cytochrome P4503A4. Concomitant use of prednisone (40 mg/day for the first 14 days of nevirapine administration) has been associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, the use of prednisone to prevent nevirapine-associated rash is not recommended.

Quinidine: Decreased plasma concentrations of quinidine may be seen if coadministered with nevirapine. Use caution and monitor quinidine therapeutic concentrations if these drugs are coadministered.

Ranolazine: Ranolazine is primarily metabolized by CYP3A isoenzymes. Although not studied, coadministration of ranolazine with a CYP3A enzyme inducer such as nevirapine may result in decreased effectiveness of ranolazine. Monitor the antianginal response to ranolazine therapy closely during coadministration with CYP3A enzyme inducers.

Ribavirin: Coadministration of ribavirin and NNRTIs such as nevirapine should be done with caution as both can cause hepatic damage. NNRTIs may cause liver damage in the context of hypersensitivity reactions or by direct toxic effects. (Many studies demonstrate that nevirapine is more hepatotoxic than efavirenz.) Underlying chronic HCV infection enhances the risk of developing liver enzyme elevations in patients receiving nevirapine. Closely monitor patients for treatment-associated toxicities, especially hepatic decompensation.

Rifabutin: Rifabutin is an inducer and a substrate of the CYP3A4 isoenzyme. Rifabutin appears to be a less potent hepatic enzyme inducer than rifampin, but the clinical significance of this finding has not been determined. While interactions may be present, certain NNRTIs may be given in combination with rifabutin to adult patients under specific circumstances. When used in combination with nevirapine, the dose of rifabutin should be 300 mg daily or 300 mg three times per week. If a patient's CD4 count is > 100 cells/mm3, twice-weekly administration of rifabutin may be considered when used in combination with nevirapine.

Rifampin: Rifampin is a significant inducer of many hepatic CYP450 isoenzymes. When coadministered, using nevirapine 200 mg twice daily, nevirapine AUC decreases 20—58% and Cmin decreases 68%. While the virologic consequences of coadministration are uncertain, the potential for additive hepatotoxicity exists, therefore, use of this combination is generally not recommended. If rifampin and nevirapine are used together, more frequent monitoring of HIV viral load, CD4+ counts, and hepatic function are recommended. Nevirapine and rifampin should be used in combination only if clearly indicated, when no other options exist, and when careful clinical and virologic monitoring are possible.

Rifapentine: Nevirapine should *not* be coadministered with rifapentine. A complex interaction is expected to occur, leading to altered plasma concentrations of either drug. Additionally, HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens, therefore, an alternative agent is recommended.

Sedatives/hypnotics: Nevirapine may decrease plasma concentrations of certain highly metabolized sedatives and hypnotics, including zolpidem. Caution should also be observed when discontinuing nevirapine in patients stabilized on both nevirapine and a sedative/hypnotic agent.

Sirolimus: Sirolimus is extensively metabolized by CYP3A4 in the gut and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-glycoprotein drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Agents that induce CYP3A4 and/or P-glycoprotein, such as nevirapine, may affect absorption and elimination of sirolimus leading to decreased blood concentrations. Monitor sirolimus serum concentrations carefully if nevirapine needs to be used concomitantly.

Sorafenib: Any drug that induces CYP3A4, such as nevirapine, may increase the metabolism of sorafenib and thereby decrease sorafenib concentrations and clinical effects.

St. John's wort: It appears that St. John's Wort is an inducer of hepatic cytochrome P450 enzymes, particularly CYP3A4, and it is expected that St. John's Wort may significantly decrease the plasma concentrations of nevirapine. Such reductions in plasma concentrations of these drugs could lead to HIV treatment failures or the development of viral-resistance. St. John's Wort in all forms, including teas, should *not* be coadministered with nevirapine.

Sunitinib: Concurrent administration of sunitinib with strong inducers of CYP3A4 such as nevirapine results in decreased concentrations of sunitinib and its primary active metabolite. Whenever possible selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended. Due to potential decreases in effectiveness, a dose increase should be considered when sunitinib must be administered concurrently with CYP3A4 inducers.

Tacrolimus: Nevirapine used concomitantly with tacrolimus can result in decreased whole blood concentrations of tacrolimus. Monitoring of tacrolimus whole blood concentrations is recommended if these drugs are coadministered.

Telithromycin: Telithromycin is a potent inhibitor of CYP3A4 and is expected to compete with nevirapine for metabolism, therefore administer together with caution, with careful monitoring of the patients nevirapine plasma concentrations and HIV status.

Voriconazole: If voriconazole and nevirapine are coadministered, a complex interaction occurs. Nevirapine can induce the CYP metabolism of voriconazole, causing decreased voriconazole concentrations. Voriconazole can inhibit the CYP metabolism of nevirapine, causing increased nevirapine concentrations. If nevirapine and voriconazole are coadministered, frequently monitor for nevirapine related toxicity and for antifungal efficacy.

Warfarin: A decrease in anticoagulant activity has been reported in patients receiving nevirapine concurrently with warfarin. Increased doses of warfarin were required to maintain therapeutic INR values. If nevirapine was stopped, a decreased dose of warfarin was required. The suspected mechanism of this interaction is induction of warfarin metabolism through CYP3A by nevirapine; close monitoring of the INR is recommended when starting or stopping nevirapine.

Other drugs/interactions

Caspofungin: Data suggest that coadministration of inducers or mixed inducers/inhibitors of hepatic drug clearance along with caspofungin may result in reduced caspofungin blood concentrations that may be clinically significant. According to the manufacturer, an increase in the caspofungin dose to 70 mg/day should be considered for patients not responding to 50 mg/day.

Raltegravir (HIV integrase strand transfer inhibitor): Raltegravir is a substrate of uridine diphosphate glucuronosyltransferase (UGT) 1A1. The impact of strong UGT1A1 inducers, such as rifampin, have shown decreases in plasma concentrations of raltegravir; however, the impact of other UGT1A1 inducers, such as nevirapine, is unknown.

Clinical Efficacy

Nevirapine has been investigated in randomized, prospective clinical trials combined with other antiretroviral drugs. These studies demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with other nucleoside analogue(s) and/or a protease inhibitor. In recent studies by intention-to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/ml after 48 weeks of combination antiretroviral treatment.

Clincal trials establishing efficacy

Clinical trial BI 1090 was a placebo-controlled, double-blind, randomized trial in HIV-1 infected patients (n = 2,249) with < 200 CD4+ cells at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve patients. Treatment doses were nevirapine 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 patients (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The patients (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV infection, with a median baseline CD4+ cell count of 96 cells/mm3 and a baseline HIV RNA of 4.58 log10 copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint study. Prior to unblinding the trial, the primary endpoint was changed to proportion of patients with HIV RNA <50 copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in the Table below.

BI 1090 Outcomes through 48 weeks

Outcome	NEVIRAPINE (N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV RNA <50 copies/mL	18.0	1.6
Treatment Failure	82.0	98.4
Never suppressed viral load	44.6	66.4
Virologic failure after response	7.2	4.3
CDC category C event or death	9.6	11.2
Added antiretroviral therapy[1] while <50 copies/mL	5.0	0.9
Discontinued trial therapy due to AE	7.0	5.9
Discontinued trial <48 weeks[2]	8.5	9.8

[1] including change to open-label NVP
[2] includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

The change from baseline in CD4+ cell count through one year of therapy was significantly greater for the Nevirapine group compared to the placebo group for the overall study population (64 cells/mm3 vs 22 cells/mm3, respectively), as well as for patients who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm3 vs 25 cells/mm3, respectively).

At two years into the study, 16% of subjects on Nevirapine had experienced class C CDC events as compared to 21% of subjects on the control arm.

Trial BI 1046 (the Italy, Netherlands, Canada, and Australia Study, or "INCAS") was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected patients with CD4+ cell counts of 200-600 at baseline. BI 1046 compared treatment with nevirapine + zidovudine + didanosine to nevirapine + zidovudine and zidovudine + didanosine. Treatment doses were Nevirapine at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The patients had mean baseline HIV RNA of 4.41 log10 copies/mL (25,704 copies/mL) and mean baseline CD4+ cell count of 376 cells/mm3. The primary endpoint was the proportion of patients with HIV-RNA < 400 copies/mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for patients treated with nevirapine + zidovudine + didanosine, 19% for patients treated with zidovudine + didanosine, and 0% for patients treated with nevirapine + zidovudine. CD4+ cell counts in the nevirapine + zidovudine + didanosine group increased above baseline by a mean of 139 cells/mm3 at one year, significantly greater than the increase of 87 cells/mm3 in the zidovudine + didanosine patients. The nevirapine + zidovudine group mean decreased by 6 cells/mm3 below baseline.

Resistance
HIV-1 resistance to nevirapine involves the development of mutations in the reverse transcriptase gene at positions 100, 103, 106, 108, 181, 188 and 190 (www.iasusa.org). The K103N or Y188L mutation alone prevents clinical utility of nevirapine. The V106M mutation is more common in HIV-1 subtype C than subtype B and confers cross-resistance to nevirapine and efavirenz.

Rapid emergence of resistance to NNRTIs, including nevirapine, is likely to occur in case of virological failure.

Patients who are infected with known nevirapine-resistant HIV or patients who have previously experienced virological failure on a nevirapine- or efavirenz-containing regimen may not respond sufficiently to further treatment with a combination regimen containing nevirapine or efavirenz.

Perinatal Transmission
Nevirapine, given to pregnant mothers in labor who have not received standard combination antiretroviral therapy during pregnancy, prevents vertical transmission of HIV-1 infection. A single dose of 200 mg of nevirapine given at the onset of labor to the mother and 2 mg/kg given to the infant within 72 hours of birth is highly efffective in reducing mother-to-child transmission of HIV-1. No benefit from additional intrapartum/newborn nevirapine was demonstrated when women received prenatal care and antenatal ART, and elective cesarean section was made available.

Single-dose use of nevirapine leads to a high rate of nevirapine resistance (17).

Clinical studies in special populations

Kidney dysfunction
In subjects with end-stage renal disease requiring hemodialysis an additional 200 mg dose of nevirapine following each hemodialysis treatment should be given to offset the effects of dialysis on nevirapine clearance. Patients with creatinine clearance ≥ 20 ml/min do not require an adjustment in nevirapine dosing.

Liver dysfunction
Nevirapine should not be used in patients with severe liver disease (Child-Pugh Classification Score > 7) or pre-treatment liver enzymes > 5 times upper limit of normal (ULN).

Clinical Safety
See the Summary of Product Characteristics, Part 4, Sections 4.4 and 4.8, in this Public Assessment Report, for a detailed discussion of warnings and precautions in relation to clinical use of nevirapine as well as a list of undesirable effects organized by body systems and frequency.

Overdose
There is no known antidote for nevirapine overdose. Nevirapine overdose ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases, and weight loss. All effects subsided following discontinuation of nevirapine.

5. Benefit / risk assessment and overall conclusion.

Quality
The quality of Nevirapine is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Nevirapine has shown to be bioequivalent to the reference listed drug (RLD) Viramune®.

Efficacy and Safety
Nevirapine is considered effective and safe to use when the guidances and restrictions presented in the Summary of Product Characteristics (Part 4 of this Public Assessment Report) are taken into consideration.

Benefit / Risk Assessment
Based on USFDA assessments of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Nevirapine Tablets 200 mg was considered acceptable for the following indication: HIV infection, used in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA tentative approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of this product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

For further information about this medicinal product, please contact:
Justina A. Molzon, M.S. Pharm, J.D.
Associate Director for International Programs
U. S. Food and Drug Administration
Center for Drug Evaluation and Research
Building 51, Room 6118
10903 New Hampshire Ave.
Silver Spring, MD 20993 USA
justina.molzon@fda.hhs.gov