CONSUMER INFORMATION
Product Monograph Part III

PrAPTIVUS®
tipranavir
250 mg capsule

Boehringer Ingelheim (Canada) Ltd.

Submission Control No. 098651

The Consumer Information Section (Part III) of the Product Monograph for APTIVUS has been submitted by the drug sponsor and is attached for your information.

The attached version accompanied the Notice of Compliance issued on November 21, 2005, and does not necessarily reflect the most current information for the product.

For the most up-to-date product information, please consult your health care professional.

Due to the fact that the information originated with an organization that is not subject to the *Official Languages Act*, the document may only appear in the language in which it was written. Translations of the document are the responsibility of the sponsor involved.

PART III: CONSUMER INFORMATION

[Pr]Aptivus®, 250 mg
(Tipranavir) Capsules

This leaflet is part III of a three-part "Product Monograph" published when APTIVUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APTIVUS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Read this information carefully before you start taking APTIVUS. Read it again each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor. You and your doctor should discuss APTIVUS when you start taking your medicine and at regular checkups. You should stay under a doctor's care when using APTIVUS. Do not change treatment or stop treatment without first talking to your doctor. Ask your doctor if you have any questions about APTIVUS.

Before taking your medicine, make sure you have received the correct medicine. Compare the name of the product stated above with the name of the product on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe you have been given the wrong medication.

In addition, since APTIVUS must be taken together with Norvir® (ritonavir), please read the Patient Information for Norvir® (ritonavir).

What the medication is used for:
APTIVUS is a medicine to treat adults with Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome). APTIVUS must always be taken with Norvir® (ritonavir) and with other anti-HIV medicines to treat people with HIV infection.

What it does:
HIV infection destroys CD4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

APTIVUS blocks HIV protease, an enzyme which is needed for HIV to multiply (make more virus). APTIVUS reduces the amount of HIV in your blood and increases the number of T cells. Reducing the amount of HIV in the blood reduces the risk of death or infections that happen when your immune system is weak (opportunistic infections).

When it should not be used:
Do not take APTIVUS:

- If you are hypersensitive (allergic) to tipranavir, ritonavir, or any of the other ingredients of APTIVUS or ritonavir (Norvir®) (**see What the important nonmedicinal ingredients are and ritonavir product monograph)**;
- If you have moderate to severe liver problems;
- If you are currently taking any of the following medications:
  - dihydroergotamine, ergonovine, ergotamine and methylergonovine
  - triazolam
  - astemizole
  - pimozide
  - cisapride (no longer marketed in Canada)
  - terfenadine
  - midazolam
  - amiodarone
  - bepridil
  - flecainide
  - propafenone
  - quinidine
  - vardenafil

Do not take APTIVUS with rifampin, as it may lower the amount of APTIVUS in your blood and make it less effective.

Do not take APTIVUS with St. John's wort (*hypericum perforatum*), a herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease APTIVUS levels and lead to an increase in HIV and possible resistance to APTIVUS or resistance to other anti-HIV medications.

Do not take APTIVUS with the cholesterol-lowering medicines lovastatin or simvastatin because of possible serious reactions.

What the medicinal ingredient is:
APTIVUS capsules contain the active ingredient called tipranavir.

What the important nonmedicinal ingredients are:
Inactive ingredients include Cremophor® EL, ethanol, mono/diglycerides of caprylic/capric acid, propyl gallate, propylene glycol, purified water, and trometamol.

Capsule shell: gelatin, iron oxide red, propylene glycol, purified water, 'sorbitol special glycerin blend' (d-sorbitol, 1,4-sorbitan, mannitol and glycerin) and titanium dioxide.

Black printing ink: ammonium hydroxide, ethylacetate, iron oxide black, isopropyl alcohol, Macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA 35 alcohol.

What dosage forms it comes in:
APTIVUS capsules are available in 250 mg strength.

WARNINGS AND PRECAUTIONS

Patients taking APTIVUS, together with 200 mg Norvir® (ritonavir), may develop severe liver disease that can cause death. If you have chronic hepatitis B or C infection you

have an increased chance of developing liver problems (See Side Effects and What to do About Them).

APTIVUS does not cure HIV infection or AIDS. The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infection, which may necessitate further evaluation and treatment. Therefore, it is very important that you stay under the care of your doctor.

APTIVUS does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

APTIVUS can cause dangerous and life-threatening interactions if taken with certain other medicines. Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements (see INTERACTIONS WITH THIS MEDICATION).

Women taking birth control pills need to use another method of birth control. APTIVUS makes birth control pills work less well.

BEFORE you use APTIVUS talk to your doctor or pharmacist:

- *If you are pregnant or planning to become pregnant:* The effects of APTIVUS on pregnant women or their unborn babies are not known. If you are pregnant, APTIVUS should only be taken after careful discussion with your doctor. Tell your doctor immediately if you become pregnant.
- *If you are breast-feeding:* Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV infection, there is a chance that HIV can be transmitted through breast-feeding.
- *If you are using estrogens for birth control or hormone replacement:* Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking APTIVUS.
- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination while taking APTIVUS.
- *If you have hemophilia:* Patients taking protease inhibitors may have increased bleeding.

INTERACTIONS WITH THIS MEDICATION

APTIVUS may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or planning to take before you take APTIVUS (See **"When it should not be used"**).

- Not all medicines can be safely taken with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS

Know all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. Keep a list of the medicines you take. Show this list to all your doctors and pharmacists anytime you get a new medicine. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

Medicines that require dosage adjustments:

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking APTIVUS.

- The blood levels of the HIV protease inhibitors Invirase® or Fortovase® (saquinavir), Agenerase® (amprenavir), and Kaletra® (lopinavir) are decreased when combined with APTIVUS taken together with Norvir® (ritonavir). Your doctor needs to carefully consider whether to treat you with combinations of APTIVUS and these protease inhibitors.
- Fluconazole (e.g. Diflucan®) increases the blood levels of APTIVUS. Consequently, fluconazole doses greater than 200mg/day are not recommended if taken together with APTIVUS.
- Ketoconazole (e.g. Nizoral®) and itraconazole (e.g. Sporanox®) should be used with caution. Doses of these medicines greater than 200mg/day are not recommended if taken together with APTIVUS.
- If you have kidney disease and you are taking both clarithromycin (e.g. Biaxin®) and APTIVUS, your doctor should reduce the dose of clarithromycin based on the extent of your kidney disease.
- APTIVUS may interact with medicines used to treat erectile dysfunction and lead to dangerous side effects or serious problems. These medicines are: sildenafil (Viagra®) and tadalafil (Cialis®). Vardenafil (Levitra®) should not be used with APTIVUS. Before you take any of these medicines with APTIVUS talk to your doctor.
- If you are taking selective serotonin reuptake inhibitors (SSRIs – medications for depression), the dose may have to be adjusted by your doctor.
- If you are taking methadone and APTIVUS, the dose of methadone may need to be increased. Ask your doctor.

- If you are taking meperidine (e.g. Demerol®) and APTIVUS, a dose increase and long-term use of meperidine are not recommended. Discuss this with your doctor.
- APTIVUS taken together with ritonavir (Norvir®) can reduce the effectiveness of oral contraceptives and may be associated with a rash. If you are taking oral contraceptives ("the pill") to prevent pregnancy, you should use an additional or different type of contraceptive (e.g. condoms) if you are taking APTIVUS.
- If you are taking desipiramine and APTIVUS, the dose of desipiramine may have to be decreased by your doctor.
- If you are taking theophylline and APTIVUS, the dose of theophylline may have to be increased by your doctor.
- If you are taking the cholesterol-lowering medication, atorvastatin (Lipitor®) and APTIVUS, the dose of atorvastatin may have to be decreased by your doctor or you may have to be switched to another cholesterol-lowering medication.
- If you are taking the antibiotic rifabutin (Mycobutin®) and APTIVUS, your dose of rifabutin will be reduced by your doctor.
- If you are taking both Videx® (didanosine) and APTIVUS, Videx® should be taken at least two hours after taking APTIVUS.
- If you are taking antacids and APTIVUS, consideration should be given to separating the dosing of these two drugs by 2 hours.
- Your doctor will use caution if you have to take concomitant non nucleoside reverse transcriptase inhibitors (efavirenz or nevirapine) because currently there are limited data on the use of these medicines with APTIVUS.
- APTIVUS capsules contain alcohol. Talk with your doctor if you are taking or planning to take metronidazole or disulfiram. An interaction between the alcohol content of APTIVUS and either of these two medicines can lead to severe side effects.

PROPER USE OF THIS MEDICATION

Usual dose:
Always take APTIVUS exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. **It is essential that you take APTIVUS together with Norvir® (ritonavir).**

If you are taking APTIVUS capsules, the usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules) of ritonavir (Norvir®), twice per day. The capsules should always be taken by mouth, and swallowed whole and not chewed. APTIVUS must also always be taken in combination with other antiretroviral medicines, for which you should be sure to follow the directions from your doctor or pharmacist.

Always take APTIVUS with food at all times to improve tolerability.

Do not change your dose or stop taking APTIVUS without first talking with your doctor.

It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your combination antiretroviral medicines and reduce the chances of developing antiretroviral resistance. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking APTIVUS correctly, as described.

When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The virus may develop resistance to APTIVUS and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give APTIVUS to others or take medicine prescribed for someone else.

You should stay under a doctor's care when taking APTIVUS. Do not change your treatment or stop treatment without first talking with your doctor.

You must take APTIVUS every day exactly as your doctor prescribed it. The dose of APTIVUS may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the medication bottle label. Due to the need for co-administration of APTIVUS with Norvir® (ritonavir), please refer to the Norvir® Patient Information for directions on its use and precautionary measures.

Overdose:
You should IMMEDIATELY contact either your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:
If you forget to take APTIVUS within 5 hours of your dosing schedule, take the next dose of APTIVUS, together with Norvir® (ritonavir), as soon as possible. If a dose is missed by more than 5 hours do not take a double dose to make up for the forgotten individual doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APTIVUS can have side effects. It may be difficult to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that you tell your doctor about any changes in your health. The following list of side effects is **not** complete. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The most commonly reported side effects of moderate severity that are thought to be drug-related are mostly associated with the gastrointestinal tract and include diarrhea, nausea, vomiting and abdominal pain. Other commonly reported side effects are tiredness and headache. Women taking oral contraceptives may get a mild skin rash.

Blood tests in patients taking APTIVUS may show possible liver problems. Patients with liver disease such as Hepatitis B and Hepatitis C who take APTIVUS may have worsening liver disease. Liver problems including liver failure and death have occurred in patients taking APTIVUS. In studies, it is unclear if APTIVUS caused these liver problems because some patients had other illnesses or were taking other medicines at the time. Patients with signs or symptoms of hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation**.** If you notice the signs or symptoms of hepatitis (fever, malaise, nausea, vomiting, abdominal pain, fatigue, jaundice) you should inform your doctor as soon as possible. Your doctor should use caution when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of hepatitis. Your doctor may consider increased liver monitoring.

Rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

Some patients taking APTIVUS have large increases in triglycerides and cholesterol (fat in the blood). The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.

Diabetes and high blood sugar (hyperglycemia) can occur in patients taking protease inhibitors such as APTIVUS. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medicine while others need new diabetes medicine.

In some individuals, treatment with protease inhibitors may cause changes in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck (the "buffalo hump").

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, 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, hyperlipidemia (increased fats in the blood) and resistance to insulin.

In patients with hemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

There have been other side effects in patients taking APTIVUS. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

(For more details see text)

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Hyperlipidemia (increased fats in the blood)		✓
	Rash		✓
Uncommon	Diabetes, high blood sugar, resistance to insulin and symptoms		✓
	Increased bleeding in those with hemophilia		✓
	Liver problems		✓

This is not a complete list of side effects. For any unexpected effects while taking APTIVUS contact your doctor or pharmacist.

HOW TO STORE IT

APTIVUS capsules are pink, oblong with a black print imprint of "TPV 250". Each APTIVUS capsule contains 250 mg of the active substance tipranavir. APTIVUS is supplied in unit-of-use bottles, with a child-resistant closure, containing 120 capsules.

APTIVUS capsules should be stored at 2-8^{o}C (refrigerated). Once the bottle is opened, refrigeration of the capsules by the patient is not required if used within 60 days and stored **at controlled room temperature 15-30^{o}C.** You can write the date of opening the bottle on the label. Do not use after the expiration date stated on the bottle.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: **866-234-2345**
Toll-free fax **866-678-6789**
By email: **cadrmp@hc-sc.gc.ca**

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.boehringer-ingelheim.ca or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103 Ext. 4633 (Medical Information).

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

Last revised: November 14, 2005