PART III: CONSUMER INFORMATION

[Pr]Aptivus®
(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. 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.

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 non-medicinal ingredients are and ritonavir product monograph**);
- If you have moderate to severe liver problems;
- If you are currently taking any of the following medications:
  - alfuzosin
  - amiodarone
  - astemizole*
  - bepridil
  - cisapride*
  - colchicine if you have kidney or liver problems
  - dihydroergotamine, ergonovine, ergotamine and methylergonovine
  - flecainide
  - lovastatin
  - oral midazolam
  - pimozide
  - propafenone
  - quetiapine
  - quinidine
  - rifampin
  - sildenafil when used for pulmonary arterial hypertension (PAH)
  - simvastatin
  - St. John's wort (*Hypericum perforatum*)
  - terfenadine*
  - oral triazolam
  - vardenafil

* These drugs are currently not marketed in Canada.

Do not take APTIVUS if you have a rare hereditary condition of fructose intolerance as this product contains 50.4 mg sorbitol per maximum recommended daily dose.

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

What the important non-medicinal 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 of Norvir® (ritonavir) may develop bleeding in the brain that can cause death. You should report any unusual or unexplained bleeding to your doctor.

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, below).

APTIVUS does not cure HIV infection or AIDS. 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 capsules contain ethanol 7 % (v/v). This should be taken into account in pregnant or breast-feeding women, children, and in high-risk groups such as those with liver disease or epilepsy. Ethanol could be harmful for those suffering from alcoholism.

APTIVUS can cause dangerous and life-threatening interactions if taken with certain other medicines. Tell your doctor about all the medicines you take including those available without a prescription, vitamins, and herbal supplements (see INTERACTIONS WITH THIS MEDICATION).

Do not take the following medicines with APTIVUS/ritonavir:

- rifampin, as this may lower APTIVUS in your blood and make it less effective.
- fluticasone proprionate (e.g. Flonase®, Flovent®, Advair®) unless your doctor believes the benefit outweighs the risk.
- trazodone (e.g. Desyrel®) as APTIVUS may increase the level of trazodone in the blood. The doctor may lower the trazodone dosage.
- St. John's wort (*Hypericum perforatum*) as this may reduce APTIVUS levels and lead to increased HIV levels or the development of resistance to APTIVUS or other HIV medications.
- omeprazole or esomeprazole, unless your doctor believes the benefits outweigh the risks.
- APTIVUS makes birth control pills work less well. Talk to your doctor about other methods of birth control.
- Tell your doctor if you are allergic to sulfa drugs.

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, have had or will have surgery, or other medical conditions that increase your chance of bleeding, or are taking medicines which increase your chance of bleeding (e.g, anticoagulants, antiplatement medication, or vitamin E supplements):* you may have an increased chance of bleeding.

INTERACTIONS WITH THIS MEDICATION

APTIVUS may interact with other medicines. Tell your doctor about all the medicines you take including those available without a prescription, herbal supplements and natural health products. You should keep a list of all the medicines that you take.

The following medicines may require your healthcare provider to either monitor your therapy or to change the dose of either APTIVUS or the other medicine:

- bupropion (antidepressant)
- bosentan
- boceprevir
- telaprevir
- etravirine
- salmeterol
- rilpivirine

- colchicine if you have kidney or liver problems.
- fluconazole increases the blood levels of APTIVUS; fluconazole doses greater than 200 mg/day are not recommended.
- ketoconazole and itraconazole, use with caution. Ketoconazole doses greater than 200 mg/day are not recommended.
- clarithromycin, your doctor should reduce the dose of clarithromycin based on the extent of your kidney disease.
- selective serotonin reuptake inhibitors (SSRIs – medications for depression).
- methadone, the dose of methadone may need to be increased.
- meperidine, a dose increase and long-term use of meperidine are not recommended.
- oral contraceptive ("the pill") levels may be reduced. The combination may cause a rash. You should use an additional or different type of contraceptive (e.g. condoms). You should be clinically monitored for estrogen deficiency if you are using estrogen for hormone replacement therapy.
- desipiramine may have to be decreased.
- theophylline may have to be increased.
- atorvastatin is not recommended unless at the lowest dose. Your doctor may switch you to another cholesterol-lowering medication.
- rosuvastatin, your doctor may decrease the dosage of rosuvastatin or may switch you to another cholesterol-lowering medication.
- rifabutin will be reduced.
- didanosine should be taken at least two hours after APTIVUS.
- antacids should be given as a separate does after two hours.
- warfarin and other blood thinners should be monitored.
- metronidazole or disulfiram contain alcohol and can lead to severe side effects.
- tadalafil. The use of APTIVUS/ritonavir with tadalafil, for the treatment of pulmonary arterial hypertension (PAH) is not recommended.
- carbamazepine, phenobarbital or phenytoin may make APTIVUS less effective.
- immunosuppressants (cyclosporin, tacrolimus, sirolimus) need to be monitored.
- Levels are decreased for HIV protease inhibitors such as saquinavir, amprenavir, atazanavir and lopinavir. Fosamprenavir is expected to act the same way. The use of these inhibitors in combination with APTIVUS is not recommended. Your doctor needs to carefully consider whether to treat you with combinations of APTIVUS and these protease inhibitors.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Always take APTIVUS exactly as your doctor has instructed you. The dose of APTIVUS may be different for you than for other patients. You should check with your doctor or pharmacist if you are unsure. **It is essential that you take APTIVUS together with Norvir® (ritonavir),** and it is necessary to refer to the Norvir® Patient Information.

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 with plenty of liquid 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.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms. Always take the labelled medicine container with you.

Missed Dose:
If you forget to take APTIVUS, do not double the next dose, but take the next dose as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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, combination antiretroviral therapy and treatment with protease inhibitors 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. People taking anticoagulant or antiplatelet medications, or those undergoing surgery may have an increased risk of bleeding while taking this treatment. Bleeding in the brain has occurred in patients treated with APTIVUS, together with Norvir® (ritonavir), in clinical trials and can lead to permanent disability or death. Many of the patients experiencing bleeding in the brain had other medical conditions or were receiving other medications that may have caused or contributed to it. Should any unusual or unexplained bleeding happen while you are taking this treatment, seek immediate advice from your doctor.

Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

Other side effects may occur with APTIVUS. Ask your doctor or pharmacist for more information about this or any other symptoms that may develop or if symptoms persist or worsen.

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)**		**T**
	Rash		**T**
Uncommon	**Diabetes, high blood sugar, resistance to insulin and symptoms**		**T**
	Increased bleeding		**T**
	Liver problems		**T**

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

Ability to drive and operate machinery:
No studies on the effects on the ability to drive and use machines have been performed for APTIVUS/ritonavir. However, dizziness, sleepiness, and fatigue have been reported in some patients. If you experience fatigue, dizziness, or sleepiness, do not drive or operate machinery until these symptoms go away.

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°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°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

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

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. 84633 (Medical Information). Please visit our website to see if more up-to-date information has been posted.

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