

Package leaflet: Information for the user

Aptivus 250 mg soft capsules tipranavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aptivus is and what it is used for
2. What you need to know before you take Aptivus
3. How to take Aptivus
4. Possible side effects
5. How to store Aptivus
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If Aptivus has been prescribed for your child, please note that all information in this leaflet is addressed to your child (in this case please read “your child” instead of “you”).

1. What Aptivus is and what it is used for

Aptivus belongs to a group of medicines called protease inhibitors and is used in the treatment of Human Immunodeficiency Virus (HIV) infection. Aptivus is an inhibitor of the HIV protease enzyme which the HIV needs to multiply. By inhibiting the protease enzyme Aptivus helps control HIV infection. You must take Aptivus together with:

- low dose ritonavir (this helps Aptivus to reach a high enough level in your blood)
- other HIV medicines. Your doctor will decide which other medicines you should take. This will depend on, for example:
 - which other medicines you have already taken for HIV
 - which medicines your HIV is resistant to. If your HIV is resistant to some HIV medicines, this means that the medicine will not work so well.

Aptivus is specifically used for the treatment of HIV which is resistant to most other protease inhibitors. Before starting treatment, your doctor will have taken blood samples to test the resistance of your HIV. These tests will have confirmed that the HIV in your blood is resistant to most other protease inhibitors. Aptivus treatment is therefore appropriate for you. You should not use Aptivus if you have never received antiretroviral therapy or have other antiretroviral options available.

Aptivus capsules are indicated for:

- adolescents 12 years of age or older
- adults

2. What you need to know before you take Aptivus

You must take Aptivus in combination with low dose ritonavir and other antiretroviral medicines. It is therefore important that you know about these medicines too. You should therefore carefully read the Package Leaflets of ritonavir and your other antiretroviral medicines. If you have any further questions about ritonavir or the other medicines you are prescribed, please ask your doctor or pharmacist.

Do not take Aptivus

- if you are allergic (hypersensitive) to tipranavir or any of the other ingredients of this medicine (listed in section 6)
- if you have moderate to severe liver problems. Your doctor will take a blood sample to test how well your liver is working (your liver function). Depending on your liver function you may have to delay or stop Aptivus treatment
- if you are currently taking products containing:
 - rifampicin (used to treat tuberculosis)
 - cisapride (used to treat stomach problems)
 - pimozone or sertindole (used to treat schizophrenia)
 - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder)
 - triazolam or oral midazolam (taken by mouth). These medicines are used to treat anxiety or sleep disorders
 - ergot derivatives (used to treat headaches)
 - astemizole or terfenadine (used to treat allergies or hay fever)
 - simvastatin or lovastatin (used to lower blood cholesterol)
 - amiodarone, bepridil, flecainide, propafenone or quinidine (used to treat heart disorders)
 - metoprolol (used to treat heart failure)
 - alfuzosin and sildenafil (when used to treat a rare blood vessel disorder characterized by increased pressure in the pulmonary artery).

Do not take products containing St John's wort (a herbal remedy for depression). This may stop Aptivus from working properly.

Warnings and precautions

Talk to your doctor or pharmacist before taking Aptivus.

Tell your doctor if you have:

- type A or B haemophilia
- diabetes
- liver disease.

If you have:

- high liver function test results
- hepatitis B or C infection

you are at increased risk of severe and potentially fatal liver damage while taking antiretroviral therapy in general, including Aptivus. Your doctor will monitor your liver function by blood tests before and during Aptivus treatment. If you have liver disease or hepatitis, your doctor will decide if you need additional testing. You should inform your doctor as soon as possible if you notice the signs or symptoms of hepatitis:

- fever
- malaise (feeling generally unwell)
- nausea (upset stomach)
- vomiting
- abdominal pain
- tiredness
- jaundice (yellowing of the skin or the eyeballs)

Aptivus is not a cure for HIV infection:

You should know that you may continue to develop infections and other illnesses associated with HIV disease. You should therefore remain in regular contact with your doctor. In addition, you should know that there is still a risk of passing HIV to others through blood or sexual contact when taking Aptivus. You should therefore continue to use appropriate precautions to prevent HIV transmission. For example you should use a condom and you should not breast-feed or donate blood.

Rash:

Mild to moderate rash, including:

- hives
- rash with flat or raised small red spots
- sensitivity to the sun

have been reported in approximately 1 in 10 patients receiving Aptivus. Some patients who developed rash also had:

- joint pain or stiffness
- throat tightness
- generalized itching

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

Your doctor may decide to monitor your levels of blood lipids (fats) before and during Aptivus treatment.

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 with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Tell your doctor if you experience fainting or a sensation of abnormal heart beats. Aptivus in combination with low dose ritonavir may cause changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an ECG (electrocardiogram).

Bone problems: Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Children and adolescents

Aptivus soft capsules should not be used by children under 12 years of age.

Older people

If you are older than 65 years your doctor will exercise caution when prescribing Aptivus soft capsules to you and will closely monitor your therapy.

Other medicines and Aptivus

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

This is **very important**. If you take other medicines at the same time as Aptivus and ritonavir, this can strengthen or weaken the effect of the medicines. These effects are called interactions, and can lead to serious side effects, or prevent proper control of other conditions you may have.

Interactions with other HIV medicines:

- Abacavir and zidovudine. These belong to a class of HIV medicines called nucleoside reverse transcriptase inhibitors (NRTIs). Your doctor will only prescribe you abacavir and zidovudine if you are unable to take other NRTIs.
- Otherwise, you can take Aptivus, together with ritonavir, with other ARVs (antiretroviral drugs) including:
 - stavudine
 - lamivudine
 - tenofovir
 - didanosine: If you are taking didanosine enteric coated tablets, you should take them at least two hours before or after Aptivus
 - efavirenz
 - nevirapine
 - raltegravir.
- Protease Inhibitors (PIs): Taking Aptivus may cause large decreases in the blood levels of other HIV protease inhibitors. For example the protease inhibitors amprenavir, atazanavir, lopinavir and saquinavir will be decreased.
Taking Aptivus, with atazanavir, may cause the blood levels of Aptivus and ritonavir to increase a lot.
Your doctor will carefully consider whether to treat you with combinations of Aptivus and protease inhibitors.

Other medicines with which Aptivus may interact include:

- oral contraceptives/hormone replacement therapy (HRT): If you are taking the contraceptive pill to prevent pregnancy you should use an additional or different type of contraception (e.g. barrier contraception like condoms). Generally, it is not recommended to take Aptivus, with ritonavir, together with oral contraceptives or hormone replacement therapy (HRT). You should check with your doctor if you do wish to continue taking oral contraceptives or HRT. If you use oral contraceptives or HRT you have an increased chance of developing a skin rash while taking Aptivus. If a rash occurs, it is usually mild to moderate. You should talk to your doctor as you may need to temporarily stop taking either Aptivus or your oral contraceptives or HRT
- carbamazepine, phenobarbital and phenytoin (used to treat epilepsy). These may decrease the effectiveness of Aptivus.
- sildenafil, vardenafil, tadalafil (medicines used to produce and maintain an erection). The effects of sildenafil and vardenafil are likely to be increased if you take them with Aptivus. You should not be prescribed tadalafil until you have been taking Aptivus for 7 days or more.
- omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole (proton pump inhibitors used to reduce the gastric acid production)
- metronidazole (used to treat infections)
- disulfiram (used to treat alcohol dependence)
- buprenorphine/naloxone (medicines used to treat severe pain)
- cyclosporin, tacrolimus, sirolimus (used to prevent organ rejection (to suppress the immune system))
- warfarin (used to treat and prevent thrombosis)
- digoxin (used to treat heart arrhythmias and heart failure)
- antifungal medications including fluconazole, itraconazole, ketoconazole or voriconazole

The following medications are not recommended:

- fluticasone (used to treat asthma)
- atorvastatin (used to lower blood cholesterol)
- salmeterol (used to achieve long-term asthma control, bronchospasm prevention with COPD).
- colchicine (used to treat gout flares)
- bosentan (used to treat pulmonary artery hypertension)
- halofantrine or lumefantrine (used to treat malaria)
- tolterodine (used to treat overactive bladder (with symptoms of urinary frequency, urgency, or urge incontinence)).

Aptivus may lead to a loss of effectiveness of some medicines including:

- methadone, meperidine (pethidine), used as morphine substitutes

Your doctor may have to increase or decrease the dose of other medicines which you take together with Aptivus. Examples include:

- rifabutin and clarithromycin (antibiotics)
- theophylline (used to treat asthma)
- desipramine, trazodone and bupropion (used to treat depression; bupropion is also used for smoking cessation)
- midazolam (when given by injection); midazolam is a sedative used to treat anxiety and to help you sleep
- rosuvastatin or pravastatin (used to lower blood cholesterol).

If you take aluminium- and magnesium-based liquid antacid (used to treat dyspepsia/gastrooesophageal reflux), the time interval between Aptivus and antacid should be at least two hours.

Tell your doctor if you receive medication such as antiplatelet agents and anticoagulants, or if you are taking vitamin E. Your doctor may wish to consider certain precautionary measures in such circumstances.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. It is not known whether Aptivus may be used safely during pregnancy. You must not breast-feed your baby because it is possible that the baby can become HIV-infected through the breast milk. See also Section 2, under "Oral contraceptives/hormone replacement therapy (HRT)".

Aptivus contains very small amounts of alcohol (see *Aptivus capsules contain ethanol*).

Driving and using machines

Some of the side effects of Aptivus may affect your ability to drive or operate machinery (e.g. dizziness and sleepiness). If affected, you should not drive or operate machinery.

Aptivus capsules contain ethanol

Aptivus contains 7 % ethanol (alcohol), i.e. up to 400 mg per daily dose, equivalent to 8 ml of beer, or less than 4 ml of wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Aptivus also contains macrogolglycerol ricinoleate which may cause stomach upset and diarrhoea.

This medicine contains small amounts of sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Aptivus

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You must take Aptivus together with ritonavir.

Aptivus capsules should be taken with food.

The recommended dose for an adult or an adolescent 12 years and above is:

- 500 mg (two 250 mg capsules) Aptivus together with
 - 200 mg (two 100 mg capsules) ritonavir
- twice per day with food.

Always take this medicine in combination with other antiretroviral medicines. You should follow the instructions for these medicines within the supplied Package Leaflets.

You should continue to take Aptivus for as long as your doctor tells you.

If you take more Aptivus than you should

Inform your doctor as soon as possible if you take more than the prescribed dose of Aptivus.

If you forget to take Aptivus

If you miss a dose of Aptivus or ritonavir by more than 5 hours, wait and then take the next dose of Aptivus and ritonavir at the regularly scheduled time. If you miss a dose of Aptivus and/or ritonavir by less than 5 hours, take your missed dose immediately. Then take your next dose of Aptivus and ritonavir at the regularly scheduled time.

Do not take a double dose to make up for a forgotten capsule.

If you stop taking Aptivus

It has been shown that taking all doses at the appropriate times:

- greatly increases the effectiveness of your combination antiretroviral medicines
- reduces the chances of your HIV becoming resistant to your antiretroviral medicines

Therefore, it is important that you continue taking Aptivus correctly, as described above. Do NOT stop taking Aptivus unless your doctor instructs you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. It may be difficult to tell the difference between:

- side effects caused by Aptivus
- side effects caused by the other medicines you are also taking
- complications of HIV infection.

For this reason it is very important that you tell your doctor about any changes in your health.

Important side effects associated with Aptivus:

- Abnormal liver function
 - Hepatitis and fatty liver
 - Liver failure. This can lead to death
 - Increased blood levels of bilirubin (a breakdown product of haemoglobin)
- You should inform your doctor if you experience:
- Loss of appetite

- Nausea (upset stomach)
- Vomiting and/or jaundice
which may be symptoms of abnormal liver function
- Bleeding
 - *Bleeding in the brain. This can lead to permanent disability or death, and has occurred in some patients treated with Aptivus in clinical trials. In the majority of these patients the bleeding may have had other causes. For example they had other medical conditions or were receiving other medicine that may have caused the bleeding.

Possible side effects:

Very common: may affect more than 1 in 10 people

- Diarrhoea
- Nausea (upset stomach)

Common: may affect up to 1 in 10 people

- Vomiting
- Abdominal pain (tummy pain)
- Flatulence (when you break wind more often)
- Tiredness
- Headache
- Mild rashes e.g. with hives or with flat or raised small red spots
- Increases in blood lipid (fat) levels
- Dyspepsia

Uncommon: may affect up to 1 in 100 people

- Reduction in red and white blood cells
- Reduction in blood platelets
- Allergic (hypersensitivity) reactions
- Decreased appetite
- Diabetes
- Increased blood sugar
- Increased blood levels of cholesterol
- Sleeplessness and other sleep disorders
- Sleepiness
- Dizziness
- Numbness and/or tingling and/or pain in the feet or hands
- Breathing difficulties
- Gastrooesophageal reflux disease
- Inflammation of the pancreas
- Skin inflammation
- Itching
- Loss or gain of body fat and other changes in fat distribution (see below)
- Muscle cramp
- Muscle pain
- Kidney disease
- Flu like symptoms (feeling unwell)
- Fever
- Weight loss
- Increased blood levels of the pancreas enzyme amylase
- Increases in liver enzyme activity
- Hepatitis with liver cell damage due to influence of a toxin

Rare: may affect up to 1 in 1,000 people

- Liver failure (including fatal outcome)
- Hepatitis
- Fatty liver
- Increased blood levels of bilirubin (a breakdown product of haemoglobin)
- Dehydration (when your body does not have enough water)
- Thinning of the face
- Intracranial haemorrhage* (see above)
- Increased blood levels of the pancreas enzyme lipase

Further information on possible side effects related to combination antiretroviral treatment:

- Blood
Combination antiretroviral therapy may also cause:
 - Raised lactic acid in the blood.
 - Raised sugar in the blood. The effect of insulin (used to treat diabetics to reduce blood sugar) may be reduced.
 - Hypertriglyceridaemia (increased triglycerides (fats) in the blood)
 - Hypercholesterolaemia (increased cholesterol in the blood)
- Bleeding
 - Increased bleeding. If you have haemophilia type A and B, you may experience increased bleeding. This may be in the skin or joints. If you suffer increased bleeding you should see your doctor immediately.

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.

Muscle disorders

There have been reports of muscle pain, tenderness or weakness. These occur particularly when Aptivus or other protease inhibitors are taken together with nucleoside analogues. Rarely these muscle disorders have been serious, involving breakdown of muscle tissue (rhabdomyolysis).

Additional side effects in children and adolescents

The most common side effects were generally similar to those described in adults. Vomiting, rash and fever were observed more frequently in children than in adults.

Reporting of side effects

If you get any side effects, please talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aptivus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Once the bottle is opened the contents must be used within 60 days (stored below 25°C). You should write the date of opening the bottle on the label and/or outer carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Aptivus contains

- The active substance is tipranavir. Each capsule contains 250 mg tipranavir.
- The other ingredients are macrogolglycerol ricinoleate, ethanol (alcohol), mono/diglycerides of caprylic/capric acid, propylene glycol, purified water, trometamol and propyl gallate. The capsule shell contains gelatin, red iron oxide, propylene glycol, purified water, 'sorbitol special-glycerin blend' (d-sorbitol, 1,4 sorbitan, mannitol and glycerin) and titanium dioxide. The black printing ink contains propylene glycol, black iron oxide, polyvinyl acetate phthalate, macrogol and ammonium hydroxide.

What Aptivus looks like and contents of the pack

Aptivus soft capsules are pink coloured, with a black print imprint of 'TPV 250'. Each Aptivus capsule contains 250 mg of the active substance tipranavir. Aptivus is supplied in bottles containing 120 capsules.

Aptivus is also available as an oral solution containing 100 mg tipranavir per ml. Not all presentations may be marketed in your country.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.