

Package leaflet: Information for the user

Aptivus 100 mg/ml oral solution tipranavir

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's 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 your child takes Aptivus
3. How to take Aptivus
4. Possible side effects
5. How to store Aptivus
6. Contents of the pack and other information

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. Your child must take Aptivus together with:

- low dose ritonavir (this helps Aptivus to reach a high enough level in your child's blood)
- other HIV medicines. Your child's doctor will decide which other medicines they should take.

This will depend on, for example:

- which other medicines your child has already taken for HIV
- which medicines your child's HIV is resistant to. If your child's 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 child's doctor will have taken blood samples to test the resistance of your child's HIV. These tests will have confirmed that the HIV in your child's blood is resistant to most other protease inhibitors. Aptivus treatment is therefore appropriate for your child. Your child should not use Aptivus if they have never received antiretroviral therapy or have other antiretroviral options available.

Aptivus oral solution is indicated for:

- children from 2 to 12 years of age

2. What you need to know before your child takes Aptivus

Your child 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 child's other antiretroviral medicines. If you have any further questions about ritonavir or the other medicines your child is prescribed, please ask your child's doctor or pharmacist.

Do not give Aptivus

- if your child is allergic (hypersensitive) to tipranavir or any of the other ingredients of this medicine (listed in section 6)
- if your child has moderate to severe liver problems. Your child's doctor will take a blood sample to test how well your child's liver is working (your child's liver function). Depending on your child's liver function they may have to delay or stop Aptivus treatment
- if your child is currently taking products containing:
 - rifampicin (used to treat tuberculosis)
 - cisapride (used to treat stomach problems)
 - pimozide 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).

Your child must 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 child's doctor or pharmacist before giving Aptivus to your child.

Tell your child's doctor if they have:

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

If your child has:

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

your child is at increased risk of severe and potentially fatal liver damage while taking antiretroviral therapy in general, including Aptivus. Your child's doctor will monitor their liver function by blood tests before and during Aptivus treatment. If your child has liver disease or hepatitis, their doctor will decide if they need additional testing. You should inform your child's doctor as soon as possible if you notice your child has 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 your child may continue to develop infections and other illnesses associated with HIV disease. You should therefore remain in regular contact with your child's 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. Your child should therefore continue to use appropriate precautions to

prevent HIV transmission. For example your child should use a condom and your child 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 child's doctor if you notice changes in body fat.

Your child's doctor may decide to monitor their 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 child's 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 your child starts taking medicines for the treatment of your child's 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 child's doctor immediately to seek necessary treatment.

Tell your child's doctor if your child experiences fainting or a sensation of abnormal heart beats. Aptivus in combination with low dose ritonavir may cause changes in your child's heart rhythm and the electrical activity of your child's 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 child's doctor.

Children and adolescents

Aptivus should neither be used by children under 2 years of age nor by adolescents 12 years of age or older.

Aptivus oral solution contains vitamin E. Your child should not take any additional vitamin E supplements.

Other medicines and Aptivus

Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines, including medicines obtained without a prescription.

This is **very important**. If your child takes 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 your child 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 child's doctor will only prescribe them abacavir and zidovudine if they are unable to take other NRTIs.
- Otherwise, your child can take Aptivus, together with ritonavir, with other ARVs (antiretroviral drugs) including:
 - stavudine
 - lamivudine
 - tenofovir
 - didanosine: If your child is taking didanosine enteric coated tablets, they 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 child's doctor will carefully consider whether to treat them with combinations of Aptivus and protease inhibitors.

Other medicines with which Aptivus may interact include:

- oral contraceptives/hormone replacement therapy (HRT): If your child is taking the contraceptive pill to prevent pregnancy they 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 child's doctor if they do wish to continue taking oral contraceptives or HRT. If your child uses oral contraceptives or HRT they 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 child's doctor as they may need to temporarily stop taking either Aptivus or their 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 taken with Aptivus. Tadalafil should not be prescribed until Aptivus has been taken 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 child's doctor may have to increase or decrease the dose of other medicines which they 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 your child sleep
- rosuvastatin or pravastatin (used to lower blood cholesterol).

If your child takes 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 child's doctor if your child receives medication such as antiplatelet agents and anticoagulants, or if your child is taking vitamin E. Your child's doctor may wish to consider certain precautionary measures in such circumstances.

Pregnancy, breast-feeding and fertility

If your child is pregnant or breast-feeding, you think your child may be pregnant or is planning to have a baby, ask your child's doctor or pharmacist for advice before giving this medicine. It is not known whether Aptivus may be used safely during pregnancy. Your child must not breast-feed the 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)".

Driving and using machines

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

3. How to take Aptivus

Always give your child this medicine exactly as the doctor has told him/her. Check with your child's doctor or pharmacist if you are not sure. Your child must take Aptivus together with ritonavir.

Aptivus oral solution should be taken with food.

The dose for children, age 2 to 12 years, will be calculated by the doctor. This will be based on the child's body surface area in metres squared. The dose for children should not exceed 5 ml (500 mg) twice a day. Be sure your child's doctor clearly informs you what the correct dose for your child should be. You should measure the exact dose using the supplied measuring syringe and adapter, as follows:

1. Check that the oral solution is clear (see below).
2. Open the bottle by pressing down on the cap and turning it in an anti-clockwise direction.
3. Remove the syringe cap covering the tip of the syringe (the cap will not be attached if this is the first time you are using the syringe).

4. Insert the syringe into the adapter located in the neck of the bottle. Make sure the syringe is tightly inserted. The maximum volume you can withdraw at one time is 5 ml (equivalent to 500 mg tipranavir), which is the maximum single dose for a child with BSA (Calculated body surface area) $> 1.33 \text{ m}^2$
5. Turn the bottle upside down and gently withdraw the required amount of Aptivus oral solution.
6. Gently empty Aptivus oral solution from the syringe into your child's mouth.
7. After use of the syringe, replace the syringe cap.

Before giving Aptivus you should check that the oral solution is clear. Crystals may be seen as a paper-thin layer at the bottom of the bottle when it is stored upright. There may be other particles at the bottom of the bottle. A small amount of crystals does not affect the strength or safety of your child's medicine.

You should return the bottle to your child's pharmacist or doctor for a replacement as soon as possible if:

- there is more than a thin layer of crystals at the bottom of the bottle, or
- you are uncertain about the amount of crystals you see or
- any other particles are visible.

Until you exchange the bottle, please continue to give your child their usual doses of Aptivus oral solution.

Your child will always have to take Aptivus in combination with other antiretroviral medicines. You should follow the instructions for these medicines within the supplied Package Leaflets.

Your child should continue to take Aptivus for as long as your child's doctor tells him/her. At the age of 12 years, children treated with Aptivus should be switched from the oral solution to the capsules.

If your child takes more Aptivus than he/she should

Inform your child's doctor as soon as possible if they take more than the prescribed dose of Aptivus.

If your child forgets to take Aptivus

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

Do not give a double dose to make up for a forgotten dose.

If your child stops taking Aptivus

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

- greatly increases the effectiveness of your child's combination antiretroviral medicines
- reduces the chances of your child's HIV becoming resistant to his/her antiretroviral medicines.

Therefore, it is important that your child continues taking Aptivus correctly, as described above. Your child must NOT stop taking Aptivus unless your child's doctor instructs to do so.

If you have any further questions on the use of this medicine, ask your child's 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 your child is also taking
- complications of HIV infection.

For this reason it is very important that you tell your child's doctor about any changes in their 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 child's doctor if they experience:
 - Loss of appetite
 - Nausea (upset stomach)
 - Vomiting and/or jaundicewhich 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 (breaking 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 the 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 your child has haemophilia type A and B, they may experience increased bleeding. This may be in the skin or joints. If your child suffers increased bleeding you should see your child's 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 your child gets any side effects, please talk to your child's 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.

Do not store below 15°C. Do not refrigerate or freeze. Once the bottle is opened your child should use the medicine within 60 days. You should write the date of opening the bottle on the label and/or outer carton. Keep the container in the outer carton.

If you notice more than a thin layer of crystals at the bottom of the bottle you should:

- give the next dose
- return the bottle to the pharmacist or doctor as soon as possible for a fresh supply.

Do not throw away any medicines via wastewater or household waste. Ask your child's 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 ml contains 100 mg tipranavir.
- The other ingredients are macrogol, vitamin E polyethylene glycol succinate, purified water, propylene glycol, mono/diglycerides of caprylic/capric acid, sucralose, ascorbic acid, Butter Mint and Butter Toffee flavourings.

What Aptivus looks like and contents of the pack

Aptivus oral solution is a clear yellow liquid.

Aptivus oral solution is supplied in amber glass bottles containing 95 ml of oral solution. A 5 ml syringe and adapter is supplied for dosing.

Aptivus is also available as soft capsules.

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 (EMA) web site: <http://www.ema.europa.eu>.