Applicant/PHRC: ***Hetero Drugs South Africa (Pty) Ltd***

*Product proprietary name****: TONATADIN 400/50***

Dosage form and strength: ***Film coated tablets and 400 /50 mg***

FINAL PATIENT INFORMATION LEAFLET FOR TONATADIN

WARNING:

If you are taking TONATADIN with some medicines used to treat allergies, medicines used to relieve anxiety and/or trouble sleeping, medicines used to correct irregular heartbeat and medicines used to treat migraine headache they may cause serious adverse events.

SCHEDULING STATUS: S4

TONATADIN 400/50 film coated tablets

Darunavir ethanolate and Ritonavir USP

Contains no sugar

Read all of this leaflet carefully before you start taking TONATADIN

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- TONATADIN has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What TONATADIN is and what it is used for
2. What you need to know before you take TONATADIN
3. How to take TONATADIN
4. Possible side effects
5. How to store TONATADIN
6. Contents of the pack and other information

1. What TONATADIN is and what it is used for

TONATADIN contains active substances called darunavir and ritonavir. TONATADIN is an antiretroviral medicine. It belongs to a group called protease inhibitors. TONATADIN works by reducing the amount of Human Immunodeficiency Virus (HIV) in your body. This will improve your immune system and reduce the risk of developing illnesses linked to HIV infection.

TONATADIN is used in combination with other antiretroviral medicines to treat adults who are infected by HIV and who have developed resistance to other antiretroviral medicines.

2. What you need to know before you take TONATADIN

Do not take TONATADIN:

- if you are hypersensitive (allergic) to darunavir, ritonavir or any of the other ingredients of TONATADIN (listed in section 6).
- if you have severe liver disease.

Do not take TONATADIN with any of the following medicines

- medicines to treat tuberculosis (*rifampicin, rifabutin*)
- medicines to treat high blood pressure as a result of problems with your lungs (*sildenafil, bosentan*)
- medicines to treat migraine and headaches (*dihydroergotamine*, *ergonovine, ergotamine, methylergonovine*)
- herbal products containing St John's wort (e.g. for depression)
- medicines to treat high cholesterol (*lovastatin and simvastatin*)
- medicines to treat psychiatric conditions such as schizophrenia (*pimozide*)
- medicines to treat trouble with sleeping and/or anxiety (*midazolam or triazolam*)
- medicines to treat fungal infections (*ketoconazole, itraconazole*, *voriconazole*)
- medicines to treat convulsions (epilepsy) (*phenobarbitone or phenytoin*)
- medicines to treat allergy symptoms (*astemizole*)

- medicines to treat gout if you have liver or kidney problems (*colchicine*)
- medicines to treat prostate problems (*alfuzosin*)
- medicines to treat some stomach conditions (*cisapride*)
- medicines to treat hepatitis C virus (*boceprevir, telaprevir*)
- medicines to treat narcotic dependence (*buprenorphine/naloxone*)
- medicines used to correct irregular heart beat (*amiodarone, bepridil, encainide, flecainide, propafenone, quinidine, digoxin*)
- medicines used to treat asthma (*salmeterol*)

If you are taking any of these, discuss it with your doctor.

Warnings and precautions

Take special care with TONATADIN:

TONATADIN must be taken together with food. TONATADIN is not a cure for HIV infection. TONATADIN does not reduce the risk of passing HIV to others through sexual contact or blood contaminations. Therefore, you must continue to use appropriate precautions, such as condoms.

People taking TONATADIN may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

Contact your doctor immediately if the following is experienced:

- severe rash
- sulphonamide (antimicrobial used to treat certain infections) allergy.

Make sure that you check the following points and tell your doctor if any of these apply to you.

- Tell your doctor if you have had **problems with your liver before**. Your doctor may evaluate how severe your liver disease is before deciding if you can take TONATADIN.
- Tell your doctor if you have **diabetes**. Anti-HIV medicines such as TONATADIN may increase sugar levels in the blood.

- Tell your doctor immediately if you notice any **symptoms of infection**. In some patients with advanced HIV and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started.
- Tell your doctor if you **notice changes in body fat**. Redistribution, accumulation or loss of body fat may occur in patients receiving a receiving a combination of

  antiretroviral medicines.
- Tell your doctor if you have **haemophilia (bleeding disease)**. Anti-HIV medicines, such as TONATADIN, may increase the risk of bleeding.
- Tell your doctor if you experience joint aches and pain, joint stiffness or difficulty in movement.
- Tell your doctor if you are allergic to sulpha medicines.
- Some patients taking TONATADIN can develop serious **problems with their pancreas** (pancreatitis), which may cause death. Tell your doctor as soon as possible if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.
- Blood tests in patients taking TONATADIN may show possible liver problems. People with liver disease such as **Hepatitis B and Hepatitis C** who take TONATADIN may have worsening liver disease. Liver problems including rare cases of death have occurred in patients taking TONATADIN. It is unclear if TONATADIN caused these liver problems because some patients had other illnesses or were taking other medicines.
- Some patients have large increases in **triglycerides and cholesterol** (fats in the blood).
- **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.

Other medicines and TONATADIN

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)

There are some medicines that you must not combine with TONATADIN. These are mentioned above under the heading:

"Do not take TONATADIN with any of the following medicines". Tell your doctor if you take any other anti-HIV medicines. TONATADIN can be combined with some other anti-HIV medicines while other combinations are not recommended.

Tell your doctor if you take:

- medicines to prevent seizures (*carbamazepine*)
- steroids (*dexamethasone*)
- medicines for heart disease or high blood pressure (*amiodarone, bepridil, felodipine, lignocaine, nifedipine, nicardipine, quinidine, digoxin*)
- medicines used to reduce clotting of the blood (*warfarin*)
- oestrogen based hormonal contraceptives. TONATADIN might reduce the effectiveness of hormonal contraceptives. Therefore, alternative methods of non-

  hormonal contraception are recommended.
- medicines to lower cholesterol levels (e.g. *atorvastatin, pravastatin and rosuvastatin*). The risk of muscle tissue disorder might be increased. Atorvastatin, pravastatin or rosuvastatin, at a reduced starting dose, could be used.
- medicines for your immune system (*ciclosporin, tacrolimus, sirolimus*). Your doctor might want to do some additional tests.

- medicines to control asthma (fluticasone and salmeterol)
- medicines for erectile dysfunction (*sildenafil, vardenafil, tadalafil*)
- antibiotics (*clarithromycin*)
- medicines to treat depression and anxiety (*paroxetine,sertraline*)
- medicines to treat narcotic dependence (*methadone*)
- medicines to treat gout or familial Mediterranean fever (*colchicine*)
- a combination medicine to treat malaria (*artemether/lumefantrine*).
- Talk to your doctor if you are taking or are planning to take fluticasone propionate. Taking fluticasone propionate and TONATADIN can increase the levels of fluticasone in your blood and could cause serious side effects.
- If you are taking rifabutin, your doctor may lower the dose of rifabutin.
- If you are taking both didanosine and TONATADIN, the dosage times of didanosine and TONATADIN should be separated by at least 2.5 hours.
- Tell your doctor if you are taking rifampin as it may reduce blood levels of TONATADIN. (see “Do not take [PRODUCT NAME”])

TONATADIN with food, drink and alcohol

TONATADIN must be taken together with food.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, please consult your doctor, pharmacist or other health care provider for advice before taking TONATADIN.

Do not take TONATADIN during pregnancy and breastfeeding. The safe use of TONATADIN in pregnancy and

during breastfeeding is not known.

Studies in animals do not indicate direct harmful effects of darunavir with respect to pregnancy, birth or development after birth.

There is a large information on the use of ritonavir during pregnancy. In general, pregnant mothers received ritonavir after the first three months of pregnancy at a lower dose (booster) along with other protease inhibitors. Ritonavir did not appear to increase the chance of developing birth defects compared to the general population.

Driving and using machines

Sleepiness and dizziness are known undesirable effects of TONATADIN which may interfere with the ability to perform potentially hazardous tasks like driving a car or operating heavy machinery.

3. How to take TONATADIN

Do not share medicines prescribed for you with any other person. Always take TONATADIN exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose of TONATADIN is two tablets once daily. You must take TONATADIN every day and always in combination with food at approximately the same time of day.

TONATADIN cannot work properly without food. You must eat a meal or snack 30 minutes before you take your TONATADIN. The type of food is not important.

Swallow the tablet with a drink such as water, milk, or any other nutritional drink. Even if you feel better, do not stop taking TONATADIN without talking to your doctor. Make sure that you always have enough TONATADIN tablets available so that you don’t run out. For example, in case you cannot return home, need to travel or stay in a hospital.

Removing the child resistant cap

The plastic bottle comes with a child resistant cap and should be opened as follows:

- Push the plastic screw cap down while turning it counterclockwise.
- Remove the unscrewed cap.

If you take more TONATADIN than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take TONATADIN

If you notice within 12 hours, you must take your tablet immediately. Always take with food. If you notice after 12 hours, then take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

TONATADIN can have side effects.

Not all side effects reported for TONATADIN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking TONATADIN, please consult your doctor, pharmacist or other health care professional for advice.

If any of the following happens, stop taking TONATADIN and tell your doctor immediately or go to the casualty department of the nearest hospital:

- severe rash with blisters
- rash or itching with swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing.

These are all very serious effects. If you have them, you may have had a serious allergic reaction to TONATADIN. You may need urgent medical attention.

Speak to your doctor immediately or go to the casualty department of your nearest hospital if you experience any of the following side effects:

- symptoms of infection or inflammation after the start of treatment (immune reconstitution inflammatory syndrome)
- inflammation of the liver or pancreas (symptoms may include abdominal pain, nausea and vomiting)
- diabetes

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- headache
- vomiting, nausea
- diarrhoea, stomach pain
- rash
- high cholesterol and other fats in the blood
- high blood sugar
- Weight loss
- Dehydration, increase in cholestrol, gout, swelling of hands and feet
- Agitation, confusion, mood alteration, nervousness
- Tingling sensation or numbness in the hands, feet or around the lips and mouth.
- Bad taste in the mouth; dizziness
- Blurred vision, painful eye, sensitivity to light
- Low blood pressure and feeling faint, when getting up,
- increase in heart beat/rate
- Cough
- Stomach ache, vomiting, diarrhoea, nausea, dry mouth,
- wind, indigestion, mouth ulcer

- Muscular pain
- Joint pain and back pain
- Increase/decrease in urination, reduced kidney function
- Feeling weak/tired, fever
- Changes in liver function tests
- Flushing, feeling hot

Less frequent

- Changes in body fats (fat redistribution)
- Loss of appetite
- Abdominal swelling, indigestion, flatulence
- Itching
- Muscle pain
- Moss of strength and energy, tiredness
- Increase in pancreatic enzymes
- Changes in blood test results, Low levels of blood platelets
- High levels of sugar in the blood
- Buzzing/roaring sound in the ear, Pain in the ear,
- Imbalance
- Abnormal dream, difficulty in paying attention, convulsions (fits)
- Change in the heart rate, fainting
- Shortness of breath, nose bleeding
- Decreased sexual drive

TONATADIN may change some values of your blood chemistry. These can be seen in the results of blood tests. Yourdoctor will explain these to you. In some patients, TONATADINhas been reported to cause a severe or life-threatening rash. In_patients taking TONATADIN and raltegravir, rashes (generally mild or moderate) may occur

more frequently than in patients taking either medicine separately. Contact your doctor if you develop a rash. Your doctor will advise you whether your symptoms can be managed on therapy or whether TONATADIN should be stopped. TONATADIN should not be taken if you suffer from liver problems.

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

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via "**6.04 Adverse Drug Reactions Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/publications/Index/8 /. By reporting side effects, you can help provide more Information on the safety of TONATADIN.

5 How to store TONATADIN

Store all medicines out of reach of children

Store at or below 25 °C

Store in the original package

Protect from light/ moisture

Do not use after the expiry date stated on the label

Return all unused medicine to your pharmacist

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What TONATADIN contains

- The active substances are drunavir ethanolate and ritonavir.
- Silicifide microcrystalline cellulose
- Crosprovidone
- Colloidal silicon dioxide
- Magnesium stearate

- Copovidone
- Sorbitan monolaurate
- Dibasic calcium phosphate anhydrous
- Sodium stearyl fumarate

Composition of Opadry yellow 16C82767

- HPMC/Hypromellose 6cP
- Titanium dioxide
- Macrogol/PEG 400
- HPMC/Hypromellose 15cP
- Hydroxypropyl cellulose
- Iron oxide yellow
- Talc
- Macrogol/PEG 3350
- Colloidal anhydrous silica
- Polysorbate 80

What TONATADIN looks like and contents of the pack

30's count HDPE container

High density polyethylene container 100 cc with 38 mm Neck (heavy weight) with a child resistant plastic cap with pulp liners 38 mm with a desiccant canister 2,0 g, silica gel

56's and 60's count HDPE container

High density polyethylene container 150 cc with 38 mm Neck (heavy weight) with a child resistant plastic caps with pulp liners 38 mm with a desiccant canister 2,0 g, silica gel

120's count HDPE container

High density polyethylene container 300 cc with 53 mm Neck (heavy weight) with a child resistant plastic cap with pulp liners 53 mm with a desiccant canister 2,0 g, silica gel

Holder of Certificate of Registration

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Access to the corresponding Professional Information

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