PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS (PREPARATIONS) 1986

This medicine is marketed upon doctor's prescription only

ATOZET® 10 mg/10 mg
ATOZET® 10 mg/20 mg
ATOZET® 10 mg/40 mg
ATOZET® 10 mg/80 mg
Film-coated tablets

Each film-coated tablet contains:
Ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 10 mg, 20 mg, 40 mg or 80 mg.

For a list of inactive ingredients see section 6 "Further information". See also section 2.8, “Important information about some of the ingredients of ATOZET”.

Read all of this leaflet carefully before you start taking this medicine.
- This leaflet contains concise information about ATOZET. If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.
- ATOZET is intended for treatment of adults above 18 years of age.

1. WHAT ATOZET IS INTENDED FOR?

ATOZET is used in combination with a diet,
- for the treatment of primary hypercholesterolaemia [heterozygous familial and non-familial] or to decrease elevated fat levels in the blood (mixed hyperlipidaemia) in adult patients:
    - that are not well controlled with a statin alone; or
    - are already treated with statin and ezetimibe

- for the treatment of adult patients with a hereditary illness (homozygous familial hypercholesterolaemia). The treatment may be given in combination with other treatments.

- If you have heart disease, to reduce the risk of cardiovascular events (as heart attack, stroke, surgery to increase heart blood flow, or hospitalisation for chest pain).

Therapeutic group: Ezetimibe belongs to a group of medicines called *CAI* (Cholesterol absorption Inhibitors), which inhibits the intestinal absorption of cholesterol. Atorvastatin belongs to a group of medicines called statins, which are HMG-CoA reductase enzyme inhibitors.

ATOZET works to reduce your cholesterol in two ways. It reduces cholesterol absorption in your digestive tract, as well as the amount of cholesterol your body makes by itself.

Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol.

LDL cholesterol is often called “bad” cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or

block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke.

HDL cholesterol is often called “good” cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease.

Triglycerides are another form of fat in your blood that may increase your risk for heart disease.

ATOZET does not help you lose weight.

2. BEFORE YOU USE ATOZET

2.1 Do not use ATOZET if:

- you are hypersensitive (allergic) to ezetimibe, atorvastatin or any of the other ingredients in ATOZET (for a list of inactive ingredients, see section 6 "Further information")
- you have or have ever had a disease that affects the liver
- you have had any unexplained abnormal blood tests for liver function
- you are a woman able to have children and are not using reliable contraception
- you are pregnant, trying to become pregnant or are breast-feeding
- you use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C.

2.2 Special warnings concerning use of ATOZET

Before starting treatment with ATOZET, tell your doctor if:

- you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes
- you have kidney problems
- you have an under-active thyroid gland (hypothyroidism)
- you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems
- you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other “statin” or “fibrate” medicines)
- you regularly drink a large amount of alcohol
- you have a history of liver disease
- you are older than 70 years
- you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product
- you are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and ATOZET can lead to serious muscle problems (rhabdomyolysis)

Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ATOZET. This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. Atorvastatin is known to cause muscle problems, and cases of muscle problems have also been reported with ezetimibe.

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

Check with your doctor or pharmacist before taking ATOZET**:**

- if you have severe respiratory failure.

If any of these apply to you (or you are not sure), talk to your doctor or pharmacist before taking ATOZET because your doctor will need to carry out a blood test before and possibly during your ATOZET treatment to identify your risk of muscle-related side effects. The risk of muscle-related side effects, e.g. rhabdomyolysis, is known to increase when certain medicines are taken at the same time (see section 2.4, “Interactions with other medicines”).

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

Tell your doctor about all your medical conditions including allergies.

The combined use of ATOZET and fibrates (medicines for lowering cholesterol) should be avoided since the combined use of ATOZET and fibrates has not been studied.

2.3 Children and adolescents
ATOZET is not intended for children and adolescents.

2.4 Interactions with other medicines
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should tell the attending doctor or pharmacist.
There are some medicines that may change the effect of ATOZET or their effect may be changed by ATOZET (see section 3 “How to take ATOZET?”). This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side effects, including the severe side effect of muscle wasting known as “rhabdomyolysis” described in section 4 “Side effects”:

- ciclosporin (a medicine often used in organ transplant patients)
- erythromycin, clarithromycin, telithromycin, fusidic acid**, rifampicin (medicines for bacterial infections)
- ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole (medicines for fungal infections)
- gemfibrozil, other fibrates, nicotinic acid, colestipol, cholestyramine (medicines for regulating lipid levels)
- some calcium channel blockers used for angina or high blood pressure, e.g., amlodipine, diltiazem
- digoxin, verapamil, amiodarone (medicines to regulate your heart rhythm)
- medicines used in the treatment of HIV, e.g., ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir, etc. (medicines for AIDS)
- some medicines used in the treatment of hepatitis C, e.g., telaprevir, boceprevir and the combination of elbasvir/grazoprevir
- daptomycin (a medicine used to treat complicated skin and skin structure infections and bacteraemia).

  ****If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart ATOZET. Taking ATOZET with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4 “Side effects”.**

- Other medicines known to interact with ATOZET
  - oral contraceptives (medicines for preventing pregnancy)
  - stiripentol (an anticonvulsant medicine for epilepsy)
  - cimetidine (a medicine used for heartburn and peptic ulcers)
  - phenazone (a painkiller)
  - antacids (indigestion products containing aluminium or magnesium)

- warfarin, phenprocoumon, acenocoumarol or fluindione (medicines to prevent blood clots)
- colchicine (used to treat gout)
- St John's wort (a medicine to treat depression).

2.5 Taking ATOZET with food, drink and alcohol
See section 3 for instructions on how to take ATOZET. Please note the following:

Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of ATOZET.

Alcohol
Avoid drinking too much alcohol while taking this medicine. See section 2.2, “Special warnings concerning use of ATOZET” for details.

2.6 Pregnancy and breast-feeding
Do not take ATOZET if you are pregnant, are trying to get pregnant or think you may be pregnant.
Do not take ATOZET if you are able to become pregnant unless you use reliable contraceptive measures. If you get pregnant while taking ATOZET, stop taking it immediately and tell your doctor.

Do not take ATOZET if you are breast-feeding.

The safety of ATOZET during pregnancy and breast-feeding has not yet been proven.

Ask your doctor or pharmacist for advice before taking this medicine.

2.7 Driving and using machines
ATOZET is not expected to interfere with your ability to drive or to use machinery. However, it should be taken into account that some people may get dizzy after taking ATOZET.

2.8 Important information about some of the ingredients of ATOZET
- ATOZET tablets contain a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product (see also section 6, “Further information”).
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. HOW TO TAKE ATOZET?
Always use ATOZET according to the doctor’s instructions. You should check with your doctor or pharmacist if you are not sure regarding the dosage and treatment regimen of ATOZET.
Your doctor will determine the appropriate tablet strength for you, depending on your current treatment and your personal risk status.
The dosage and treatment regimen will be determined by the doctor only.
- Before starting ATOZET, you should be on a diet to lower your cholesterol.
- You should keep on this cholesterol-lowering diet while taking ATOZET.

The usually recommended dose is:
One ATOZET tablet by mouth once a day.
Take ATOZET at any time of the day. You can take it with or without food.
Do not exceed the recommended dose.
There is no information regarding crushing/splitting/chewing.

If your doctor has prescribed ATOZET along with cholestyramine or any other bile acid sequestrant (medicines for lowering cholesterol), you should take ATOZET at least 2 hours before or 4 hours after taking the bile acid sequestrant.

If you take more ATOZET than you should
Please contact your doctor or pharmacist.
If you have taken an overdose or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

If you forget to take ATOZET
Do not take an extra dose; just take your normal amount of ATOZET at the usual time the next day.

Adhere to the treatment regimen recommended by the doctor.
Even if there is an improvement in your health, do not discontinue use of this medicine before consulting your doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take your medicine. Wear glasses if you need them.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. SIDE EFFECTS
As with any medicine, the use of ATOZET may cause side effects in some of the users.
Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

If you experience any of the following serious side effects or symptoms, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.
- serious allergic reaction which causes swelling of the face, tongue and throat that can cause great difficulty in breathing

- serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes, genitals and fever; skin rash with pink-red blotches, especially on palms of hands or soles of feet, which may blister

- muscle weakness, tenderness, pain or rupture, red-brown discolouration of urine and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems

- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells)

You should consult your doctor as soon as possible if you experience problems with unexpected or unusual bleeding or bruising, because this may be suggestive of a liver complaint.

Additional side effects:
Common side effects (may affect up to 1 in 10 patients):
- diarrhoea
- muscle aches

Uncommon side effects (may affect up to 1 in 100 patients):
- the flu
- depression; trouble sleeping; sleep disorder
- dizziness; headache; tingling sensation

- slow heart beat
- hot flush
- shortness of breath
- abdominal pain; abdominal bloating; constipation; indigestion; flatulence; frequent bowel movements; inflammation of the stomach; nausea; stomach discomfort; upset stomach
- acne; hives
- joint pain; back pain; leg cramps; muscle fatigue, spasms, or weakness; pain in arms and legs
- unusual weakness; feeling tired or unwell; swelling especially in the ankles (oedema)
- elevations in some laboratory blood tests of liver or muscle (CK) function
- weight gain

Additionally, the following side effects have been reported in people taking ATOZET, or ezetimibe or atorvastatin tablets:

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which requires treatment immediately)
- raised red rash, sometimes with target-shaped lesions
- liver problems
- cough
- heartburn
- decreased appetite; loss of appetite
- high blood pressure
- skin rash and itching; allergic reactions including rash and hives
- tendon injury
- gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting)
- inflammation of the pancreas often with severe abdominal pain
- reduction in blood cell counts, which may cause bruising/bleeding (thrombocytopenia)
- inflammation of the nasal passages; nose bleed
- neck pain; pain; chest pain; pain in the throat
- increases and decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels)
- having nightmares
- numbness or tingling in the fingers and toes
- reduction of sensation to pain or touch
- change in sense of taste; dry mouth
- loss of memory
- ringing in the ears; hearing loss
- vomiting
- belching
- hair loss
- raised body temperature
- urine tests that are positive for white blood cells
- blurred vision; visual disturbances
- gynaecomastia (breast enlargement in men and women)

Possible side effects reported while using other medicines of the statin group:

- sexual difficulties
- depression
- breathing problems including persistent cough and/or shortness of breath or fever

- diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.
- muscle pain, tenderness, or weakness that is constant and particularly if, at the same time, you feel unwell or have a high temperature that may not go away after stopping ATOZET (frequency not known).

If a side effect appears, if any of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by using the link "Adverse Drug Reactions Report" at the home page of the Ministry of Health's website (www.health.gov.il) which refers to the online side effects reporting form, or by using the link:
/https://sideeffects.health.gov.il

5. HOW TO STORE ATOZET?

- Avoid Poisoning! This medicine, as all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor!
- Do not use ATOZET after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.
- **Storage conditions**: Store below 30ºC. Store in the original package in order to protect from oxygen.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredients the medicine also contains:
lactose monohydrate; cellulose, microcrystalline; calcium carbonate; croscarmellose sodium; povidone; hydroxypropyl cellulose; magnesium stearate; sodium lauryl sulfate; silica, colloidal anhydrous; polysorbate 80.
The film coating contains: hypromellose, macrogol, titanium dioxide, talc.

What ATOZET film-coated tablets look like and contents of the pack
ATOZET are film-coated tablets, capsule-shaped, biconvex, white to off white.
ATOZET 10 mg/10 mg tablets: “257” debossed on one side.
ATOZET 10 mg/20 mg tablets: “333” debossed on one side.
ATOZET 10 mg/40 mg tablets: “337” debossed on one side.
ATOZET 10 mg/80 mg tablets: “357” debossed on one side.

Pack sizes: 10, 30 tablets in blisters.
Not all pack sizes may be marketed.

Marketing authorization holder:
Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

Manufacturer:

MERCK SHARP & DOHME CORP., New-Jersey, USA.

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Drug registration no. listed in the official registry of the Ministry of Health:
ATOZET® 10 mg/10 mg: 156-65-34490
ATOZET® 10 mg/20 mg: 156-66-34492
ATOZET® 10 mg/40 mg: 156-67-34494
ATOZET® 10 mg/80 mg: 156-68-34495