פברואר 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: אטוזט

ATOZET® 10 mg/10 mg (Ezetimibe 10mg/ Atorvastatin 10 mg)
ATOZET® 10 mg/20 mg (Ezetimibe 10mg/ Atorvastatin 20 mg)
ATOZET® 10 mg/40 mg (Ezetimibe 10mg/ Atorvastatin 40 mg)
ATOZET® 10 mg/80 mg (Ezetimibe 10mg/ Atorvastatin 80 mg)

Dosage Form: Tablets
Composition: Desogestrel 150 mcg; Ethinylestradiol 20 mcg

חברת מרק שארפ ודוהם ישראל (MSD) מבקשת ליידע על עדכון העלונים לרופא ולצרכן של אטוזט.

להלן לשון ההתוויה המאושרת לתכשיר:

Hypercholesterolaemia
ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate

- **patients not appropriately controlled with a statin alone**
- **patients already treated with a statin and ezetimibe**

Homozygous Familial Hypercholesterolaemia (HoFH)
ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

Prevention of Cardiovascular Events
ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

עדכונים מהותיים בעלון לרופא:
טקסט מהותי שהתווסף מודגש בקו תחתון.

4.3 Contraindications

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ATOZET is contraindicated in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

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Due to the atorvastatin component of ATOZET, the risk of rhabdomyolysis is increased when ATOZET is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. , ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, or niacin. If possible, alternative (non-

interacting) therapies should be considered instead of these medicinal products. (See section 4.8.)

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Daptomycin
Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend ATOZET in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the prescribing information of Daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) and for further guidance related to monitoring (see section 4.5.).

4.5 Interaction with other medicinal products and other forms of interaction

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Pharmacodynamic interactions
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of ATOZET with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).

…
Atorvastatin

CYP3A4 inhibitors: Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g., ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with ATOZET cannot be avoided, lower starting and maximum doses of ATOZET should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

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Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin. Consideration should be given to
suspending ATOZET temporarily in patients taking daptomycin unless the benefits of concomitant
administration outweigh the risk (see section 4.4).

4.6 Fertility, pregnancy and lactation

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ATOZET is contraindicated during pregnancy (see section 4.3). No clinical data are available on the use of ATOZET during pregnancy. ATOZET should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ATOZET should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

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Atorvastatin

Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3). Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis.

Ezetimibe

No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

4.8 Undesirable effects

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Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of ATOZET (or co-administration of ezetimibe and atorvastatin equivalent to ATOZET) or ezetimibe or atorvastatin or reported from post-marketing use with ATOZET or ezetimibe or atorvastatin are listed in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common ≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000).; and not known (cannot be estimated from the available data).

Table 3
Adverse Reactions

System organ class Frequency	**Adverse reaction**
Infections and infestations	
Uncommon	influenza
Not known	nasopharyngitis
Blood and lymphatic system disorders	
Not known	thrombocytopaenia
Immune system disorders	
Not known	hypersensitivity, including anaphylaxis, angioedema, rash, and urticaria
Metabolism and nutrition disorders	
Not known	decreased appetite; anorexia; hyperglycaemia; hypoglycaemia
Psychiatric disorders	
Uncommon	depression; insomnia; sleep disorder
Not known	nightmares
Nervous system disorders	
Uncommon	dizziness; dysgeusia; headache; paraesthesia
Not known	hypoesthesia; amnesia; peripheral neuropathy

Eye disorders	
Not known	vision blurred; visual disturbance
Ear and labyrinth disorders	
Not known	tinnitus; hearing loss
Cardiac disorders	
Uncommon	sinus bradycardia
Vascular disorders	
Uncommon	hot flush
Not known	hypertension
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea
Not known	cough; pharyngolaryngeal pain; epistaxis
Gastrointestinal disorders	
Common	diarrhoea
Uncommon	abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort
Not known	pancreatitis; gastro-oesophageal reflux disease; eructation; vomiting; dry mouth
Hepatobiliary disorders	
Not known	hepatitis; cholelithiasis; cholecystitis; cholestasis; fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	
Uncommon	acne; urticaria
Not known	alopecia; skin rash; pruritus; erythema multiforme; angioneurotic oedema; dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity
Not known	myopathy/rhabdomyolysis; muscle rupture; tendinopathy, sometimes complicated by rupture; neck pain; joint swelling; myositis; lupus-like syndrome; immune-mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders	
Not known	gynecomastia
General disorders and administration site conditions	
Uncommon	asthenia; fatigue; malaise; oedema
Not known	chest pain; pain; peripheral oedema; pyrexia
Investigations	
Uncommon	ALT and/or AST increased; alkaline phosphatase increased; blood creatine phosphokinase (CPK) increased; gamma-glutamyltransferase increased; hepatic enzyme increased; liver function test abnormal; weight increased
Not known	white blood cells urine positive

<u>עדכונים מהותיים בעלון לצרכנית:</u>
טקסט מהותי שהתווסף מודגש בקו תחתון.

2.1 אל תיטול אטוזט אם:

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<u>הינך משתמש בשילוב של גלקאפרביר/פיברנטאסביר בטיפול של צהבת C</u>

2.3 נטילת תרופות אחרות

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- תרופות מסויימות לטיפול בדלקת כבד מסוג C, לדוגמא, טלאפרוויר, <u>בוקפרביר והשילוב של גלקאפרביר/פיברנטאסביר.</u>

4 תופעות לוואי

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- <u>חולשה,</u> רגישות, כאב <u>או קרע בשריר, שינוי צבע אדום-חום בשתן</u> ובמיוחד, אם באותו זמן, אתה מרגיש לא טוב או שיש לך חום גבוה, הדבר עלול להיגרם על ידי פירוק שריר חריג, אשר עשוי להיות מסכן-חיים ולהוביל לבעיות בכליות

- <u>תסמונת דמויית מחלת זאבת (הכוללת פריחה, הפרעות במפרקים, והשפעות על תאי הדם).</u>

בעלונים לרופא ולצרכן היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו.
העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, חברת MSD, בטלפון 09-9533333.

ATOZET® מופצת ע"י חברת נובולוג בע"מ.

בברכה,
מיכל סרפר
רוקחת ממונה
MSD ישראל

References:
Israeli approved PC 4/2017, updated according to the guidelines of the Ministry of Health in February 2020
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