VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Hypercholesterolemia (or hyperlipidaemia) refers to high blood cholesterol levels. Cholesterol is a waxy, fatty substance (also known as lipid) that the body needs the appropriate amounts of to work properly. It is obtained from food and is also made by the liver.

There are a few different types of cholesterol, including:

- Total cholesterol (all the cholesterol combined; Total-C)
- Low-density lipoprotein cholesterol (LDL-C): also called "bad" cholesterol because it is the main source of cholesterol build-up and blockage in the blood vessels.
- High-density lipoprotein cholesterol (HDL-C) also called "good" cholesterol because it helps keep cholesterol from building up in the blood vessels.
- Triglycerides: are types of fat found in blood. Body uses them for energy.

High blood cholesterol levels, particularly high LDL-C and triglyceride levels, may lead to a build-up of cholesterol and fat along the inner walls of the blood vessels of the heart (coronary heart disease) and brain (cerebrovascular disease) which increases the risk of heart disease and stroke.

The most common cause of hypercholesterolemia is an interaction between genes and dietary and other factors, such as smoking and physical inactivity. This is called primary non-familial hypercholesterolemia. Primary non-familial hypercholesterolemia affects about 34% of men (ranging from 21% - 41% in different regions) and 40% in women (ranging from 26% - 47% in different regions). [Ref. 5.4: 03QJDC]

Homozygous and heterozygous familial hypercholesterolaemia (HoFH and HeFH) are genetic diseases which are passed down from parents which cause very high levels of bad cholesterol. The defect makes the body unable to remove LDL-C from the blood. Most people with FH inherit a defective gene for FH from only one parent and are therefore called heterozygous (HeFH). Rarely, a person may inherit the genetic defect from both parents and thus have homozygous FH (HoFH). About 1 per 500 people [Ref. 5.4: 03PJWM, 03QJFY, 03QJFZ] and 1 per 1,000,000 [Ref. 5.4: 03QJFZ] people have HeFH and HoFH respectively. It is more commonly found in Afrikaner, French Canadians, Ashkenazi Jews, and Lebanese populations [Ref. 5.4: 03QKW2]. The rates of HeFH and HoFH are the same for both men and women. Individuals with familial hypercholesterolemia tend to get coronary artery disease at earlier ages and those with HoFH tend to have a decreased life span.

The potential health risk due to all type of hypercholesterolaemia includes risk of heart attack, stroke, chest pain (angina), reduced blood flow to heart (ischaemic heart disease), and death related to heart and blood vessel (cardiovascular) problems. According to the World Health Organization over 30% of deaths worldwide are related to cardiovascular disease [Ref. 5.4: 03QJG9]. Cardiovascular disease causes nearly half of all deaths in Europe [Ref. 5.4: 03QJD3].

Ezetimibe/atorvastatin is also used to reduce the risk of cardiovascular events in patients with coronary heart disease and a history of a heart attack or unstable angina.. Coronary heart disease (CHD) is the result of plaque buildup in the arteries that supply oxygen-rich blood to your heart. The buildup of plaque occurs over many years as a result of hypercholesterolemia and leads to blockages restricting blood flow to the heart. If the flow of oxygen-rich blood to your heart muscle is reduced or blocked, angina or a heart attack can occur. Angina is chest pain or discomfort. A heart attack occurs if the flow of oxygen-rich blood to a section of heart muscle is cut off causing damage to the heart. About 6.2% of adults in the United States [Ref. 5.4: 042MCN] and 5.7% of men and 3.5% of women in the UK [Ref. 5.4: 04CGKK] have CHD.

VI.2.2 Summary of Treatment Benefits

Efficacy is the capacity of a drug to produce a desired effect.

Atozet is a combination medicine containing the active ingredients atorvastatin and ezetimibe. Atorvastatin belongs to a class of medicines called HMG-CoA reductase inhibitors (statins) which work by slowing down the production of cholesterol by the liver. Ezetimibe works by preventing the absorption of cholesterol in the small intestine.

This medicine is used together with lifestyle changes (diet, weight loss and exercise) in adults with heterozygous or homozygous FH and primary non-familial hypercholesterolemia.

The addition of ezetimibe to atorvastatin leads to increased lowering of blood cholesterol levels. A study randomly assigned 628 patients with high blood cholesterol levels to: ezetimibe alone, atorvastatin alone (testing all doses), placebo (pill without active medicine) or combined therapy with ezetimibe and atorvastatin. After 12 weeks of therapy, total-C, LDL-C and triglycerides were lowered to a greater extent in patients on both atorvastatin and ezetimibe (total-C decreased by 41%, LDL-C decreased by 56% and triglycerides decreased by 33%) as compared to atorvastatin alone (total-C 32%, LDL-C 44% and triglycerides 24%), ezetimibe alone (total-C 14%, LDL-C 20% and triglycerides 5%) or placebo (total-C increased by 4%, LDL-C increased by 4% and triglycerides decreased by 6%). In addition, HDL-C level increased to a greater extent in the patients with both atorvastatin and ezetimibe (7%) as compared to atorvastatin alone (4%), ezetimibe alone (4%) or placebo (4%). Two more studies, involving 740 patients with high blood cholesterol levels, gave similar results.

In another 14-week study, 621 patients on dietary treatment with heterozygous FH, heart disease, or more than two risk factors for heart disease were assigned to either both atorvastatin and ezetimibe or atorvastatin alone. The reduction in cholesterol levels was more in patients on both medicines (total-C 17%, LDL-C 24% and triglycerides 9%) than in patients who had took a double amount of atorvastatin (total-C 6%, LDL-C 9% and triglycerides 4%). In addition, after 4 weeks, more patients on the combined medicines reached a good level of LDL-C goal as compared to those receiving double the atorvastatin dose in the atorvastatin-alone group.

Ezetimibe/atorvastatin was tested in 36 patients with homozygous FH in a 12-week study. Using both ezetimibe and atorvastatin (at doses of 10/80 mg and 10/40 mg) resulted in a

reduction of LDL-C of 25% at high dose and 19% at lower dose, as compared to a 2% reduction in patients in whom the dose of atorvastatin was doubled (from 40 mg to 80 mg in the atorvastatin-alone group).

IMPROVE-IT was a randomized, double-blind, parallel group, multicenter study of ezetimibe/simvastatin (combination tablet) versus simvastatin monotherapy, designed to assess the clinical benefit of the 2 therapies in the incidence of the composite endpoint in a stabilized acute coronary syndrome (ACS) subject population. Subjects were initially randomized in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg daily and subsequently uptitrated in a blinded manner to ezetimibe./simvastatin 10/80 mg or simvastatin 80 mg daily based on LDL-C levels. The primary composite endpoint was CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either PCI or CABG occurring at least 30 days after randomized treatment assignment, and non-fatal stroke. IMPROVE-IT randomized a total of 18,144 subjects with stabilized high-risk ACS. The protocol-defined intent-to-treat (ITT) population included 9,067 subjects in the ezetimibe/simvastatin group and 9,077 subjects in the simvastatin monotherapy group. All subjects were to be followed for a minimum of 2.5 years. The median length of follow-up for the primary endpoint in the ITT population was 56.9 mos (4.7 years). Overall, the trial achieved 104,135.0 patient-years of follow-up for all-cause mortality. The study met its primary and all secondary composite efficacy endpoints and based on the design of the study, these benefits are attributable to ezetimibe. Specifically, ezetimibe/simvastatin treatment significantly reduced the incidence of the following endpoints, compared to treatment with simvastatin monotherapy:

- the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.

- the composite endpoint of death due to coronary heart disease (CHD), non-fatal myocardial infarction (MI), and urgent coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) occurring at least 30 days after randomization.

- the composite endpoint of cardiovascular death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non-fatal stroke.

VI.2.3 Unknowns Relating to Treatment Benefits

Atozet has not been studied in:

- children,
- pregnant and breastfeeding women, and
- patients with active liver disease.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Important identified risks are safety issues or undesirable effects for which there is sufficient proof of an association or link with the use of this medicine.

Table 74 provides information on the important identified risks and their preventability.

Table 74 Summary of Important Identified Risks

Risk	What is known	Preventability
Muscle injury (Rhabdomyolysis/ myopathy)	• Muscle injury is a rare but known effect of statins, including atorvastatin. • It may be mild to severe, ranging from muscle pain, tenderness and weakness to muscle inflammation (myositis) and muscle breakdown (rhabdomyolysis). • Serious cases of muscle injury were rare in clinical studies of Atozet (reported in less than 1 in 1000 patients). • How statins cause muscle injury is not known. • It is not completely known which patients are at greatest risk of developing muscle injury with Atozet use. However, muscle injury may occur more frequently in patients who: ◦ are elderly ◦ have a small body frame and are weak ◦ have low thyroid hormone levels (hypothyroidism) ◦ have diseases affecting more than one system of the body ◦ have poor kidney function ◦ are on a number of medicines ◦ have recently undergone surgery ◦ drink large quantities of alcohol ◦ are taking high doses of statins	• Patients should promptly report signs and symptoms of muscle injury, should these occur. • Creatine kinase is an enzyme that is released by damaged muscle that doctors can test for to help in checking for muscle problems. • Patients who have muscle injury should immediately discontinue treatment with this medicine.

Table 74 Summary of Important Identified Risks

Risk	What is known	Preventability
Abnormal liver function (Abnormal liver function)	• Effects on the liver, such as abnormal liver blood tests, liver inflammation, and acute or chronic liver failure, have been observed in patients treated with this medicine, but these events are uncommon. • Serious liver blood test abnormalities were rare (reported in less than 1 in 1000 patients) in clinical studies of Atozet. • Most events of abnormal liver function were mild to moderate in intensity and resolved upon stopping the medicine. • The mechanism by which abnormal liver function associated with Atozet use occurs is not known. • It is not clearly known which patients are at risk of developing abnormalities in liver function with Atozet use. However, changes in liver function are more frequently seen in patients who: ◦ are elderly ◦ are men ◦ have higher body mass index and waist circumference ◦ drink alcohol in large amounts ◦ are receiving treatment with certain medicines (such as painkillers, anti-seizure medicines, anti-tubercular medicines, herbal medications, or use illicit drugs) ◦ have liver disease (such as fatty liver disease, hepatitis B and C and other forms of liver inflammation) ◦ have certain medical conditions (such as autoimmune diseases, haemochromatosis, Wilson's disease, congestive heart failure, coeliac disease, hypothyroidism, Addison's disease and glycogen storage disease)	• Atozet should be used with caution in patients with liver impairment. • Atozet should not be used in patients with active liver disease or with unexplained persistent increases in liver function tests higher than 3 times the upper limit of normal • It is recommended to perform liver function tests before starting treatment with Atozet and whenever required during treatment.

Table 74 Summary of Important Identified Risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	• Allergic reactions, such as rashes, hives, itching, difficulty in breathing and/or swallowing, congestion of the nose, swelling of the face, tongue, throat, lips, eyes, hands and feet, may occur rarely with the use of this medicine. • Serious allergic reactions were rare in clinical studies. Serious allergic reactions may include whole body reaction (anaphylaxis), swelling of the deep layers of the skin (angioedema) or swelling of the face, tongue and throat. • Most cases of allergic reactions to Atozet were mild to moderate and resolved upon stopping the medicine.	• Atozet should not be used by patients who are allergic to ezetimibe or atorvastatin or any of the inactive ingredients of the drug product. • Patients who develop signs and symptoms of allergic reactions should promptly stop taking the medicine and seek medical attention immediately.
Drug interaction with medicines used to prevent blood clots (warfarin, phenprocoumon, acenocoumarol or fluindione; these medicines are also referred to as anticoagulants)	• A study in healthy adults showed no significant effect on warfarin levels and prothrombin time with co-administration of ezetimibe. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications. Prothrombin time and INR are blood tests used to monitor patients taking warfarin. • Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. • The effect of Atozet on the prothrombin time has not been studied.	• If warfarin, another coumarin anticoagulant, or fluindione is administered along with Atozet the INR or prothrombin time should be appropriately monitored to reduce the risk of bleeding events associated with these drugs. • Patients should talk to their doctor/pharmacist about any other medicines they are taking or might be taking.

Table 74 Summary of Important Identified Risks

Risk	What is known	Preventability
Drug interaction with medicine often used in organ transplant patients to prevent organ rejection (ciclosporin)	• Clinical studies have shown an increased level of ezetimibe in renal transplant patients taking ezetimibe and ciclosporin. In a study of healthy subjects administration of ezetimibe and ciclosporin resulted in an increase in the level of ciclosporin.	• Interactions can be prevented by avoiding the use of Atozet at the same time as ciclosporin. • Side effects due to this interaction can be prevented by monitoring the concentration of ciclosporin in the blood. • Patients should talk to their doctor/pharmacist about any other medicines they are taking or might be taking.

Important Potential Risks

Important potential risks are safety issues or undesirable effects for which there is some basis for suspicion of a link with the use of medicine of interest, but this association has not been confirmed.

Table 75 provides information on the important potential risks identified with the medicinal product.

Table 75 Summary of Important Potential Risks

Risk	What is known
Gallbladder inflammation/gallstones (Cholecystitis/cholelithiasis)	• It is unknown if gallstones/gallbladder inflammation occurs due to the use of Atozet. • Gallstones (cholelithiasis) and gallbladder inflammation (cholecystitis) have been reported to occur rarely (reported in less than 1 in 1000 patients) in clinical studies of Atozet, and no more frequently than in placebo or other comparison groups. • How gallbladder inflammation/gallstones may occur with the use of Atozet is not clearly known. In some animal studies, the ezetimibe medicine in Atozet increased the cholesterol content of bile which is made in the gallbladder. • Signs and symptoms of gallbladder inflammation and gallstones are sharp, cramping, dull or steady pain in the upper abdomen; clay-coloured stools; fever; nausea and vomiting; and yellowing of the skin and whites of the eyes (jaundice). • It is not clearly known which patients (if any) are at risk of developing gallstones/gallbladder inflammation with Atozet use. However, patients who are generally at risk of gallstones/gallbladder inflammation may have higher chances of developing gallstones/gallbladder inflammation during Atozet use. • Gallstones/gallbladder inflammation is generally seen in patients who: ◦ have a family history of gallstones/gallbladder disease ◦ are of advanced age ◦ are women ◦ are overweight or obese ◦ have recently lost weight rapidly ◦ are less physically active ◦ have metabolic syndrome (high blood sugar, high blood pressure, high triglyceride levels and a large waistline).

Table 75 Summary of Important Potential Risks

Risk	What is known
Inflammation of the pancreas (Pancreatitis)	• It is unknown if pancreatitis, or inflammation of the pancreas, occurs due to the use of Atozet. • No cases of pancreatitis were observed in clinical studies of Atozet and pancreatitis has been reported rarely with the use of the medicines in Atozet. • How pancreatitis may occur with the use of Atozet is unknown. It is also not clearly known which patients (if any) are at risk of pancreatitis with Atozet use. • Signs and symptoms of pancreatitis are pain in the upper part of the abdomen that radiates to the back; swelling and tenderness of the abdomen; nausea and vomiting; fever; and increased heart rate.
Stroke due to bleeding in the brain (Hemorrhagic stroke)	• Stroke occurs when blood supply to the brain stops. Hemorrhagic stroke is caused by a blood vessel that breaks and bleeds into the brain. • In a clinical trial, patients with a previous stroke taking atorvastatin at the highest dose had a higher incidence of hemorrhagic stroke than those who were not taking atorvastatin. It is unknown if stroke due to bleeding in the brain occurs due to the use of Atozet. • How hemorrhagic stroke may possibly be associated with Atozet is unknown. • Signs and symptoms of hemorrhagic stroke may include severe headache – sometimes in a specific area, nausea and vomiting, neck stiffness, dizziness, seizures or change in mental state (irritability, confusion and unconsciousness). • It is not clearly known which patients are at risk of hemorrhagic stroke with Atozet use. Risk factors for hemorrhagic stroke may include. ◦ older age ◦ high blood pressure ◦ use of blood thinners (such as warfarin) and antiplatelet medicines (such as acetylsalicylic acid and clopidogrel) ◦ smoking ◦ kidney dialysis ◦ use of certain drugs such as cocaine, amphetamines and phenylpropanolamine. • Patients may be able to reduce the risk of haemorrhagic stroke by keeping their blood pressure well under control and by stopping smoking.

Table 75 Summary of Important Potential Risks

Risk	What is known
Interstitial lung disease	• Interstitial lung disease refers to a group of diseases that affect the interstitium (a lace-like network of tissue that is present in both the lungs and provides support to the lungs' air sacs) of the lungs. In interstitial lung disease, thickening of the interstitium due to inflammation, scarring or extra fluid occurs • It is unknown if interstitial lung disease occurs due to the use of Atozet. • No cases of interstitial lung disease were observed in clinical studies of Atozet. • How interstitial lung disease may occur in patients treated with Atozet is unknown. It is also not clearly known which patients are at risk of interstitial lung disease with Atozet use. • Signs and symptoms of interstitial lung disease are shortness of breath, cough and weight loss.
Diabetes (New-onset diabetes)	• New onset diabetes is associated with the statin class of medicines including atorvastatin. • Diabetes describes a group of metabolic diseases in which the person has high blood sugar, either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. • New-onset diabetes refers to the onset of a condition that causes high blood sugar in a patient who previously did not have diabetes. • It is unknown if diabetes occurs due to the use of Atozet. • How diabetes may occur in patients treated with Atozet is unknown. • Signs and symptoms of diabetes are ◦ urinating more often than usual ◦ feeling very thirsty ◦ feeling hungry (even though the patient eats often) ◦ tiredness ◦ blurry vision ◦ cuts/bruises that are slow to heal, tingling ◦ weight loss ◦ tingling ◦ pain or numbness in the hands or feet.

Table 75 Summary of Important Potential Risks

Risk	What is known
	• It is not clearly known which patients are at risk of developing new-onset diabetes with Atozet use. Risk factors for the development of new-onset diabetes include ◦ older age ◦ obesity ◦ family history of diabetes ◦ a history of diabetes diagnosed during pregnancy ◦ impaired glucose metabolism ◦ physical inactivity ◦ diet. • Patients may be able to reduce the risk of new-onset diabetes by losing weight, becoming physically active and eating a healthy balanced diet.

Missing Information

Missing information is information about the safety of a medicine or pill which is not available at the time of submission of a particular risk management plan.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal (kidney) impairment) or where there is a high likelihood of off-label use (pill used for indication other than what it is approved for).

Table 76 provides missing information with the medicinal product.

Table 76 Summary of Missing Information

Missing information	What is known
Use in pregnancy and breastfeeding (Exposure during pregnancy and lactation)	• Atozet has not been studied in pregnant and breastfeeding women. • Atozet should not be used during pregnancy and breastfeeding.
Use in children less than 18 years of age	• Atozet has not been studied in children. • Since the safety and efficacy of Atozet have not been tested in children, Atozet should not be used in children.
Use in patients with moderate or severe liver problems (Exposure in patients with moderate or severe hepatic insufficiency)	• Atozet should not be used in patients with moderate or severe liver problems.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have an SPC which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the PIL. The measures in these documents are known as routine risk minimisation measures.

The SPC and the PIL for ezetimibe/atorvastatin can be found on your local Health Authority website.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned Post-Authorization Development Plan

VI.2.6.1 List of Studies in post-authorization development plan

There are no studies in the post-authorisation development plan for this medicine.

VI.2.6.2 Studies which are a condition of the marketing authorisation

There are no studies in the post-authorisation development plan for this medicine.

VI.2.7 Summary of Changes to the Risk Management Plan over Time

Table 77 Major changes to the Risk Management Plan Over Time

RMP Version	Date	Safety Concern	Comment
3	10-JUL-2014	**Important Identified Risks:** • Muscle injury (Rhabdomyolysis/ myopathy) • Abnormal liver function • Allergic reactions (Hypersensitivity) • Interstitial lung disease Diabetes (New-onset diabetes)	None
		Important Potential Risks: • Gallbladder inflammation/ gallstones (Cholecystitis/cholelithiasis) • Pancreas inflammation(Pancreatitis) • Stroke due to bleeding in the brain (Hemorrhagic stroke) • Cancer (Malignancy)Use in patients with moderate or severe liver problems (Exposure in patients with moderate or severe hepatic insufficiency)	

Table 77 Major changes to the Risk Management Plan Over Time

RMP Version	Date	Safety Concern	Comment
		Important Missing Information: • Use in pregnancy and breastfeeding (Exposure during pregnancy and lactation) • Use in children less than 18 years of age	
4	24Mar2015	Removal of cancer (malignancy) as an Important Potential Risk.	Based on results of completed trial (IMPROVE-IT).
4.1	01Oct2015	Drug interaction with warfarin, another coumarin anticoagulant or fluindione and drug interaction with ciclosporin added as important identified risks.	Administrative change; these drug interactions were included in the table of important identified and potential interactions in the previous version of the RMP (version 4.0); they were not included in any of the risk tables starting with table entitled Summary of Ongoing Safety Concerns.
		Interstitial lung disease and diabetes (new-onset diabetes) reclassified as important potential risks (formerly classified as important identified risks).	Change is consistent with company label and what is known about statins in general.
4.2	29Feb2016		Version 4.2 is an administrative update regarding the indication for use.

Key Points

- This medication is used to reduce blood cholesterol levels in patients with raised cholesterol level in blood or elevated fat levels in blood. It may also be used to reduce the risk of cardiovascular events in patients with coronary heart and a history of acute coronary syndrome.
- Muscle injury is a known risk associated with the use of Atozet. Patients should be alert to symptoms such as unexplained muscle pain, tenderness or weakness and seek medical attention immediately, should these occur.
- Abnormal liver function is a known risk associated with the use of Atozet. Periodic blood tests to check liver function are recommended during treatment with Atozet.
- This medicine should not be used by those who have moderate or severe liver problems.
- This medicine should not be used by those who have a history of allergic reactions to ezetimibe, statins or any inactive ingredient of the drug product.
- Gallstones, gallbladder inflammation, pancreas inflammation, raised blood sugar levels (including diabetes) and hemorrhagic stroke have happened in patients using Atozet.
- This medicine should not be used by pregnant or breastfeeding women and by children.