

1.8.2	Ezetimibe
Risk Management System	tablets

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Cardiovascular disease (CVD) is responsible for one-third of global deaths and is a leading and increasing contributor to the global disease burden. The costs associated with the the condition are enormous, with the cost of CVD and stroke in the US in 2007 estimated at 431.8 milliard dollar. One of the highly prevalent risk factor for CVD is hyperlipidemia or hyperlipoproteinemia including hypercholesterolemia which are extremely common in the general population. Among the dislipidemias hypercholesterolemia is the most important risk for the development of coronary heart disease and the main responsible lipoprotein in coronary atherosclerosis is low density lipoprotein (LDL) which carries the most of plasma cholesterol in the blood. The guidelines of the American Heart Association and the NCEP Adult Treatment Panel III (ATP III) define hypercholesterolemia as a blood cholesterol concentration of greater than or equal to 6.2 mmol/l (240 mg/dl). Desirable cholesterol concentrations are less than 5.2 mmol/l (200 mg/dl). The National Health and Nutrition Examination Survey III, performed from 1988- 1991, found that 26% of American adults had high blood cholesterol concentrations and 49% had desirable values. In 2001-2002 a survey found the overall prevalence of hypercholesterolemia was 47%, when hypercholesterolemia was defined as a low-density lipoprotein cholesterol level of $\geq 3.4 \text{ mmol/l} (\geq 130 \text{ mg/dl})$ [or \geq 2.6 mmol/l (\geq 100 mg/dl) if DM or CVD was present] or on treatment. Serum cholesterol concentrations vary widely throughout the world. Generally, countries associated with low serum cholesterol concentrations (eg, Japan) have lower CHD event rates, while countries associated with very high serum cholesterol concentrations (eg, Finland) have very high CHD event rates. However, some populations with similar total cholesterol levels have very different CHD event rates, as would be expected given that other risk factors (e.g. prevalence of smoking or diabetes mellitus) also influence CHD risk. The cholesterol levels in developing countries tend to increase as western dietary habits replace traditional diets.

Among adults, National Health and Nutrition Examination Survey III data (1988-1992) show more frank hypercholesterolemia among non-Hispanic white persons (19%) than Mexican Americans (15%) or non-Hispanic black persons (16%).

Hypercholesterolemia is more common in men younger than 55 years and in women older than 55 years.

In adults, hypercholesterolemia increases with advancing age.

VI.2.2 Summary of treatment benefits

The association between elevated serum cholesterol levels and risk of cardiovascular disease has been well established through a number of epidemiologic studies, such as the Framingham Heart Study and the Seven Countries Study. Multiple randomized controlled

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trials over the past two decades have consistently shown that treatment with 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in dyslipidemic patients with and without established vascular disease effectively lowers low-density lipoprotein cholesterol (LDL-C) levels and reduces major cardiovascular events. Based upon these lines of evidence, the National Cholesterol Education Program (NCEP) through the Adult Treatment Panel (ATP) III has recommended reducing LDL-C levels as the primary goal and supports the use of statins as the initial preferred therapy.8 Recent trials have suggested that more aggressive lowering of LDL-C to levels of ,70 mg/dL may result in incremental cardiovascular benefit. Therefore, ATP III was updated to include an optional LDL-C goal of ,70 mg/dL in very high-risk patients that have established cardiovascular disease with multiple cardiac risk factors.

Despite growing evidence supporting a lower-is-better approach for LDL-C, treatment with statin therapy alone may not be sufficient to achieve optimal LDL-C targets, with some patients requiring greater than a 50% reduction. Institutional surveys have shown that only two-thirds of vascular disease patients are at an LDL-C goal of, 100 mg/dL and less than a third of very highrisk patients are able to reach an LDL-C goal of, 70 mg/dL. Based upon these treatment failures, combination therapies using multiple cholesterol-lowering agents including ezetimibe in addition to statin therapy have been investigated. While ATP III recommends statin therapy as the firstline agent for the treatment of elevated LDL-C, alternative therapies such as ezetimibe, niacin, bile-acid sequestrants, and ileal bypass surgery can also effectively lower LDL-C. A recent metaanalysis has shown that these nonstatin-based treatments can lower cardiac events similar to statin therapies, with an equivalent observed relationship between degree of LDL-C lowering and reduction in coronary heart disease (CHD) risk. These data suggest that the addition of these therapies to a background of statin treatment may produce an incremental lowering of LDL-C, and possibly result in a further reduction in cardiovascular events.

VI.2.3 Unknowns relating to treatment benefits

Hepatic insufficiency

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients.

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VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Muscle Breakdown / Pain or	Patients starting therapy with	In rare cases, these situations
weakness in muscles	ezetimibe have an increased	(especially when they lead to
	risk for development of	kidney damage or heart
(Rhabdomyolysis /	muscle diseases, like pain or	problems), can be potentially
wiyopatny)	weakness in muscles	life threatening. However,
	(myopathy), or in severe	when treated in time, most of
	cases, muscle breakdown	these reactions have a good
	(rhabdomyolysis). Based on	outcome. For this reason,
	the current experiences, a	early recognition of these
	high percent of these	conditions is essential.
	reactions occurred in those	Therefore, patients should
	patients, who used Ezetimibe	contact their doctors
	together with statins (which	immediately if they
	are also drugs used to lower	experience unexplained
	blood cholesterol levels) or	muscle pain, tenderness or
	with other drugs also known	weakness, or muscle cramps
	to cause such reactions.	and stiffness, as these
	Myopathy is a condition	symptoms can draw the
	when the muscles do not	attention to these possible
	function normally resulting	undesirable effects.
	in muscular	If such a muscle disorder is
	weakness, muscle aches, like	suspected based on muscle
	pain in arms and legs,	symptoms or is confirmed by
	unusual tiredness or	medical and laboratory
	weakness, muscle cramps or	examinations, Ezetimibe
	muscle stiffness.	(and also statins or any other
	Muscle breakdown	drugs which are known to
	(rhabdomyolysis) means	also cause muscle breakdown
	such a condition in which	in patients taking these
	damaged skeletal muscle	medications simultaneously),
	tissue breaks down rapidly	should be discontinued
	and their contents release	immediately and an
	into the bloodstream. One of	appropriate treatment should
	the early complications of a	be initiated to avoid more
	muscle breakdown can be a	severe consequences.
	very high level of potassium	

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hyperkalaemia), which can lead to disturbances in the heart rhythm or in very severe cases, it can cause cardiac arrest (when the heart stops beating). In other cases, the liver can also be injured. On rare occasions, muscle breakdown resulting in kidney damage can be serious and may become a potentially lifethreatening condition. However, if recognized and treated correctly in time, these reactions often have good outcomes.Liver function disorders may occur more likely when do the statin.Liver damage, elevations in some laboratory blood test every organ in the body and of liver (Abnormal liver function)Liver function disorders may every organ in the body and oit for survival. The liver sections often have good outcomes.Liver function disorders may occur more likely when occur more likely when together with statins (which transforming and clearing his susceptible to the toxis, it is overdoses and sometimes even when introduced within medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ.Patients who currently have liver problems or whos aboratory blood test subs working. These kinds of blood test results show an abnormal liver more likely when ezetime is administered together with a statin.During treatment with tatins (which are also drugs uocur. These problems occur more likely when ezetime is administered together with a statin.Patients who currently have liver problems or whose should no		in the blood (called		
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in overdoses and sometimesblood tests might be repeated after starting treatment of ezetimibe with a statin.injure the organ.Patients who currently haveDuring Ezetimibe liver damages may occur. These problems occurliver show an abnormal liver function for a longer period without any known reason statins (which are also drugs used to lower bloodstatin.		medicinal agents, when taken	working. These kin	nds of
even when introduced within therapeutic ranges, may injure the organ.after starting treatment of ezetimibe with a statin.During treatment with Ezetimibe liver damages may occur. These problems occurPatients who currently have liver problems or whose laboratory blood test results show an abnormal liver function for a longer period without any known reason statins (which are also drugs used to lower blood		in overdoses and sometimes	blood tests might be r	repeated
therapeutic ranges, may injure the organ.ezetimibe with a statin.During treatment with Ezetimibe liver damages may occur. These problems occurPatients who currently have liver problems or whose laboratory blood test results show an abnormal liver function for a longer period without any known reason statins (which are also drugs used to lower blood		even when introduced within	after starting treatm	nent of
injure the organ.Patients who currently haveDuring treatment withliver problems or whoseEzetimibe liver damages maylaboratory blood test resultsoccur. These problems occurshow an abnormal livermore likely when ezetime isfunction for a longer periodadministered together withwithout any known reasonstatins (which are also drugsshould not take ezetimibeused to lower bloodtogether with a statin.		therapeutic ranges, may	ezetimibe with a statir	ı.
Patients who currently haveDuring treatment withEzetimibe liver damages maylaboratory blood test resultsoccur. These problems occurmore likely when ezetime isfunction for a longer periodadministered together withstatins (which are also drugsshould not take ezetimibeused to lower blood		injure the organ.		
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Ezetimibe liver damages may laboratory blood test results occur. These problems occur show an abnormal liver more likely when ezetime is function for a longer period administered together with without any known reason statins (which are also drugs should not take ezetimibe used to lower blood together with a statin.		During treatment with	liver problems or	whose
occur. These problems occurshow an abnormal livermore likely when ezetime isfunction for a longer periodadministered together withwithout any known reasonstatins (which are also drugsshould not take ezetimibeused to lower bloodtogether with a statin.		Ezetimibe liver damages may	laboratory blood test	results
more likely when ezetime is function for a longer period administered together with without any known reason statins (which are also drugs should not take ezetimibe used to lower blood together with a statin.		occur. These problems occur	show an abnormal	l liver
administered together with without any known reason statins (which are also drugs should not take ezetimibe used to lower blood together with a statin.		more likely when ezetime is	function for a longer	period
statins (which are also drugs should not take ezetimibe used to lower blood together with a statin.		administered together with	without any known	reason
used to lower blood together with a statin.		statins (which are also drugs	should not take ez	etimibe
		used to lower blood	together with a statin	-
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1.8.2	Ezetimibe	
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	cholesterol levels).	
		According to the current
	The classic symptoms of	knowledge, there is no need
	liver damage include the	to modify the standard
	following: pale stools, dark	dosage of ezetimibe in
	urine, jaundice (yellowing	patients who have mild liver
	eyes/skin), swelling of the	impairment. However, in
	abdomen, ankles and feet,	patients with moderate or
	persistent nausea/vomiting,	severe liver problems, the
	stomach/abdominal pain,	use of ezetimibe is not
	fatigue bruising In several	recommended
	cases liver function	
	alterations might not be	Patients should inform their
	accompanied with any	doctors before starting the
	symptom (called as	ezetimibe treatment if they
	asymptomatic liver function	know about any previous
	alteration)	liver diseases (or they should
		discuss it when they are not
	Liver damages can be	sure about it) and natients
	diagnosed by laboratory	should immediately seek
	blood tests called liver	medical advice if any
	function tosts which show	symptom of a liver damage
	devoted values in these	symptom of a liver damage,
	elevated values in these	like pale stools, dark urine,
	cases. In most of the cases,	Jaundice, swelling of the
	these liver function	abdomen, ankles and leet,
	the exetimite treatment is	stomach/abdominai pain,
	the ezetimide treatment is	longstanding
	stopped or sometimes even	nausea/vomiting, latigue
	when the ezetimibe treatment	and/or bruising occurs.
A 11	is continued.	
Allergic reaction	Like all medicines, ezetimibe	Patients who are allergic to
(Hypersensitivity)	can cause allergic reactions	ezetimibe or any of the other
	in patients who are	ingredients of this medicine
	susceptible for such events.	must not take this
	Allergic reactions including	medicament.
	rash and hives; raised red	Patients should always
	rash, sometimes with target-	inform their doctors about
	shaped lesions (erythema	any allergies they have
	multiforme) have been	before starting the treatment
	reported in general use.	with this product.
	Severe allergic reactions,	Patients should be advised to
	including swelling of the	remain alert for any
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1.8.2 Ezetimibe		
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	face, lips, tongue, and/or	symptoms compatible with
	throat that may cause	an allergic reaction (e.g.
	difficulty in breathing or	difficulty in breathing,
	swallowing (which requires	itching, hives and swelling
	treatment right away) have	(especially of the face and/or
	also been reported in	throat), etc.) and to stop
	connection with	ezetimibe and seek medical
	the use of ezetimibe.	advice immediately if such
	Patients who are allergic to	symptoms occur.
	ezetimibe or any of the other	
	ingredients of this medicine	
	must not take ezetimibe.	
Simultaneous use of other	A drug interaction is a	Patients should always
medications which are used	situation in which a medicine	inform their doctors about
to prevent blood clots	affects the activity of another	taking any medicines
(anticoagulants) during	drug when both are	together with ezetimibe
treatment with ezetimibe	administered together There	especially if they take any
	have been drug interactions	medicines which are used to
(Drug interaction with	reported when ezetimibe was	prevent blood clots such as
warfarin anothercoumarin	used together with medicines	warfarin phenprocoumon
anticoogulant	that prevent blood clots	acenocoumarol or fluindione
fluindiono)	(called anticoagulants like	(called anticoagulants)
numulone)	warfarin or fluindione) In	(called anticoagulants).
	these appear is laboratory test	medicines the laboratory
	alled International	hland test called IND
	Normalized Datia (IND)	(Intermetional Normalized
	Normalised Ratio (INR)	(International Normalised
	showed increased values, that	Ratio) should be regularly
	draws attention to an	checked. In some cases,
	increased risk of bleeding in	modification of the dose of
	these patients.	these medicines might be
		necessary.
Simultaneous use of	Ciclosporin is a medicine	Patients should always
ciclosporin (a medicine often	that is often used in renal	inform their doctors about
used in organ transplant	transplant patients to prevent	taking any medicines
patients) during treatment	any disorder (rejection) of	together with ezetimibe,
with ezetimibe	the transplanted foreign	especially if they take
(Drug interaction with	organ. There have been	ciclosporin, which is a
ciclosporin)	reports in which ciclosporin	medicine often used in organ
	level increased in patients	transplant patients.
	who started treatment with	Ciclosporin concentrations
	ezetimibe simultaneously.	should be regularly checked
	High level of ciclosoprin	in those patients who receive
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1.8.2	Ezetimibe
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	may cause several serious ezetimibe and ciclosporin
	side effects therefore the simultaneously.
	blood concentrations of this
	medicine should be
	monitored in patients
	receiving ezetimibe and
	ciclosporin simultaneously.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)	
Inflammation of the	Cholelithiasis is the medical term for gallstone disease.	
gallbladder/ Gallstones	Gallstones are concretions that form in the biliary tract,	
(Cholecystitis/Cholelithiasis)	usually in the gallbladder. Gallstones develop insidiously, and they may remain asymptomatic for decades.	
	Cholecystitis is the inflammation of the gallbladder, which	
	occurs most commonly due to blockage of the cystic duct	
	with gall stones leading to increased pressure in the	
	gallbladder, stagnation of bile and consecutive infection.	
	Gallbladder infections can occur with a sudden onset called	
	acute cholecystitis. On rare occasions serious complications	
	might occur like gall bladder perforation which is a rare but	
	lifethreatening complication of the gallbladder infection of	
	sudden onset or bacteria can spread rapidly back up the	
	ductal system into the liver which can result in a life-	
	threatening infection called ascending cholangitis. Therefore	
	early diagnosis and treatment of an acute cholecystitis is of	
	high priority.Chronically, gallstones in the gallbladder may	
	cause progressive fibrosis and loss of function of the	
	gallbladder, a condition known as chronic cholecystitis.	
	Gallstones and/or inflammation of the gallbladder usually	
	present with pain in the right upper quadrant of the abdomen,	
	nausea, vomiting and fever. For most patients diagnosed	
	with acute cholecystitis, the definitive treatment is surgical	
	removal of the gallbladder, called cholecystectomy.	
	Ezetimibe is often used in combination with fibrates	
	(medicines also used for lowering cholesterol). Based on	
	animal studies fibrates may increase cholesterol excretion	
	into the bile, leading to gallstone formation. In a clinical	
	study cholecystectomy was carried out more often in patients	

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1.8.2	Ezetimibe		
Risk Management System	tablets		
	who were treated with the combination of ezetimibe and		
	fenofibrate. The safety and efficacy of the combined use of		
	ezetimibe and fibrates have not been established. A risk of		
	increased gall stone formation associated with the		
	therapeutic use of ezetimibe cannot be ruled out.		
	Patients and physicians should be aware of the possible risk		
	of gallbladder diseases (gallstone formation and		
	inflammation) when fenofibrate and ezetimibe are		
	administered simultaneously. Therefore, patients should		
	always inform their doctors about taking any medicines		
	together with ezetimibe, especially if they take fibrates. If a		
	gallstone disease (cholelithiasis) is suspected in a patient		
	receiving ezetimibe and fenofibrate (on the basis of either		
	medical test results or typical symptoms), patients should contact their doctors. In these cases gallbladder investigations are indicated and this therapy should be		
	stopped.		
Inflammation of pancreas	Pancreatitis is the medical term for the inflammation of the		
	pancreas. It can be manifested with a sudden onset		
(Pancreatitis)	accompanied with intensive symptoms called acute		
	pancreatitis or can occur over several years often with		
	moderate and non-specific symptoms (especially in the first		
	period), the latter called as chronic pancreatitis.		
	Acute inflammation of the pancreas are often associated with		
	gallstones. The most common symptoms of pancreatitis are		
	severe upper abdominal burning pain radiating to the back,		
	nausea, and vomiting that is worsened with eating. Acute		
	pancreatitis might be manifested in mild or more severe form		
	with complications leading to a potentially life-threatening		
	condition.		
	After ezetimibe products were put on the market, there were		
	reports about inflammation of the pancreas (pancreatitis)		
	which occurred during treatment with ezetimibe. Patients		
	receiving ezetimibe and their doctors should be aware of the		
	possible risk of pancreatitis. If patients experience symptoms		
	typical for pancreatitis (such as severe abdominal pain which		
	radiates to the back, jaundice, fever, severe nausea nad		
	vomiting, etc.), they should immediately contact their		
	doctors, as early diagnosis and treatment of this condition is		
	essential for a better outcome.		

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1.8.2	Ezetimibe
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Missing information

Risk	What is known
Limited information on use	In the animal studies (which are generally conducted during
of ezetimibe during	a relative early phase of the drug development), ezetimibe,
pregnancy and breastfeeding	when administered alone, did not cause relevant
	malformations in the developing offspring and no direct or
(Exposure during	indirect harmful effects were seen on the pregnancy, birth or
pregnancy and lactation)	after-birth development of offspring. However, In animal
	studies simultaneous administration of ezetimibe with
	lovastatin (a medicine also used to lower blood cholesterol)
	resulted in some deaths of the developing embryos.
	Since there are no sufficient data on the safe use of the
	product during human pregnancies (since its use was not
	examined during human pregnancies), therefore taking
	ezetimibe is not recommended in women who are actually or
	might be pregnant. Ezetimibe should be given to pregnant
	women only if clearly necessary.
	Simultaneous therapy with ezetimibe and a statin is
	prohibited during pregnancy, therefore patients should not
	take ezetimibe with a statin if they are pregnant, are trying to
	get pregnant or think they may be pregnant. Patients who get
	pregnant while taking ezetimibe together with a statin
	should stop taking both medicines immediately and contact
	their doctor
	Patients who are pregnant or breast-feeding or who think
	they may be pregnant or who are planning to get pregnant
	should consult their doctors or pharmacist before starting the
	treatment with ezetimibe
Limited information on use	There is limited clinical experience about the use of
of ezetimibe in children aged	ezetimibe in adolescent nationts (aged 10-17 years old)
10 to 17 for more than 1 year	During the development of this medicine a study involving
and in children aged 6 to 10	about 250 boys and girls of 10 to 17 years of age was carried
vears for more than 12 weaks	out where the patients were treated with existing and
years for more then 12 weeks	simulation (another medicine for the treatment of high
(Limited aliniaal trial	sinvasiatin (another incurente for the treatment of flight
children and in abildren and	generally no detectable effect on growth or group
experience in children age	generally no detectable effect on growth of sexual
10 to 17 years old beyond 1	maturation in the addressent boys of girls, of any effect on
year and in children 6 to 10	mensurual cycle length in girls. However, the effects of
years old beyond 12 weeks.	ezeumide for a longer treatment period (over 33 weeks) on

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1.8.2	Ezetimibe	
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N P 1 4 · 1	anothe and control method by the start beautiful	
No clinical trial experience	growth and sexual maturation have not been studied.	
in children less than 6 years	The long-term effectiveness of the ezetimibe therapy	
of age.)	regarding its further positive effects for the adulthood in	
	The deily does of exclimite in adelegeents and children (10)	
	to 17 years of ago) is the same as for adults. The years the	
	hody absorbs, distributes and gets rid of azetimiba are	
	body absorbs, distributes and gets rid of ezetimibe are similar between children over 6 years and adulta	
	Similar between children over 6 years and adults Starting a treatment with agatimiha in children must be	
	Starting a treatment with ezetimibe in children, must be controlled by a specialist. When treating a child with the	
	combination of ezetimibe and a statin (which is also a	
	medicine used to lower blood cholesterol) the dosage	
	instructions for the statin should be considered Close	
	follow-up is recommended in this age-group.	
	There is limited data on the safe and effective use of	
	ezetimibe in children between 6 and 10 years of age, and	
	there is no available data on use of ezetimibe in children	
	younger than 6 years. During the development of this	
	medicine, the use of ezetimibe (regarding its effectiveness	
	and safety) was studied during a 12-week treatment period in	
	about 140 children of 6 to 10 years of age. However, effects	
	of ezetimibe for treatment periods over 12 weeks have not	
	been studied in this age group and the long-term	
	effectiveness of the ezetimibe therapy regarding its further	
	positive effects for the adulthood in patients below 17 years	
	of age has not been studied. Furthermore, ezetimibe has not	
	been studied in patients younger than 6 years of age.	
	There is no clinical experience with co-administration of	
	ezetimibe and a statin (another medication used for the	
	10 years of age	
	According to our current knowledge, the ways the body	
	According to our current knowledge, the ways the body	
	between children over 6 years and adults. Since there are no	
	sufficient data on the effective and safe use of ezetimibe in	
	children under 10 years of age the product is not	
	recommended in this age-group. In case ezetimibe therapy	
	would be necessary in this age group, the treatment must be	
	started under the control of a specialist and close follow-up	
	is needed.	

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1.8.2	Ezetimibe
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VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care 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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first Risk management plan.

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