Part VI: Summary of activities in the risk management plan by product

5.1 Part VI.1 Elements for summary tables in the EPAR

Table 4-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Gastrointestinal events
	Hypersensitivity events
	Hepatobiliary events
	Effect on coagulation parameters
	Hypoglycemia
	Pancreatitis
	Oxalate nephropathy
	Hypothyroidism / reduced control of hypothyroidism
	Convulsions / reduced control of epilepsy
Important potential risks	Impact on pregnancy prevention
	Inappropriate / off-label use in patients with BMI <28 kg/m^2*
	Henoch-Schonlein purpura*
	Use in patients with eating disorders*
Identified Drug-Drug Interactions	Drug-drug interaction with ciclosporin
	Drug-drug interaction with acarbose
	Drug-drug interaction with amiodarone
	Interaction with fat soluble vitamins
	Drug interaction with antiretrovirals*
Potential Drug-Drug Interactions	Drug-drug interactions with oral anticoagulants
	Drug-drug interactions with antiepileptic drugs
	Drug-drug interactions with levothyroxine / iodine salts
	Drug-drug interaction with antidepressant and antipsychotic drugs
Missing information	Use in patients with hepatic impairment
	Use in patients with renal impairment
	Use during pregnancy
	Use during lactation
	Use in children < 12 years of age
	Use in patients aged 65 years and older*

* this risk is contained only in the RMP for the 60 mg reference product

Table 4-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None.

Table 4-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None.

Table 4-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Gastrointestinal events	Guidance is given in sections 4.4 "Special warnings and precautions for use", 4.8 "Undesirable effects" and 4.2 "Posology and method of administration" of the SmPC.	None.
Hypersensitivity events	Guidance is given in is mentioned in sections 4.3. "Contraindications", and 4.8 "Undesirable effects" of the SmPC.	None
Hepatobiliary events	Guidance is given in section 4.8 "Undesirable effects" of the SmPC. Cholelithiasis: Guidance is given in the sections 4.3 "Contraindications" and 4.8 "Undesirable effects" of the SmPC.	None.
Effects on coagulation parameters	Guidance is given in sections 4.8 "Undesirable effects" of the SmPC.	None.
Hypoglycemia	Guidance is given in section 4.4 "Special warnings and precautions for use" of the SmPC.	None.
Pancreatitis	Guidance is given in section 4.8 "Undesirable effects" of the SmPC.	None.
Oxalate nephropathy	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Hypothyroidism, reduced control of hypothyroidism	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.5 "Interaction with other medicinal products and other forms of interaction "of the SmPC.	None.
Convulsions, reduced control of epilepsy	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC.	None.
Impact on pregnancy prevention	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.6 "Fertility, pregnancy and lactation" of the SmPC.	None.
Inappropriate / off-label use in patients with BMI <28 kg/m^2*	Guidance is given in section 4.1 "Therapeutic indications" of the SmPC. The PIL provides clear guidance how to determinate if subjects'BMI is under 28 and what is the weight related to a height below of which orlistat should not be used.	None.
Henoch-Schonlein purpura*	Currently available data do not support the need for risk minimization.	None.
Use in patients with eating disorder*s	Currently available data do not support the need for risk minimization.	None.
Drug-drug interactions with ciclosporin	Guidance is given in sections 4.3. "Contraindications", and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC.	None.
Drug-drug interactions with acarbose	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC.	None.
Drug-drug interactions with amiodarone	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC.	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Interactions with fat soluble vitamins	Guidance is given in sections 4.4 “Special warnings and precautions for use”, and 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.	None.
Drug-drug interaction with antiretrovirals*	The risk of drug-drug interactions with antiretrovirals is mentioned in sections 4.4. “Special warnings and precautions for use”, and 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.	None.
Drug-drug interactions with oral anticoagulants	Guidance is given in sections 4.3. “Contraindications”, and 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.	None.
Drug-drug interactions with antiepileptic drugs	Guidance is given in sections 4.4 “Special warnings and precautions for use”, and 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.	None.
Drug-drug interactions with levothyroxine / iodine salts	Guidance is given in sections 4.4 “Special warnings and precautions for use”, and 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.	None.
Drug-drug interactions with antidepressant and antipsychotic drugs	Currently available data do not support the need for risk minimization.	None.
Use in patients with hepatic impairment	Guidance is given in section 4.2 “Posology and method of administration” of the SmPC.	None.
Use in patients with renal impairment	Guidance is given in section 4.2 “Posology and method of administration” of the SmPC.	None.
Use during pregnancy	Guidance is given in sections 4.3. “Contraindications”, and 4.6 “Fertility, pregnancy and lactation” of the SmPC.	None
Use during lactation	Guidance is given in sections 4.3. “Contraindications”, and 4.6 “Fertility, pregnancy and lactation” of the SmPC.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Use in children < 12 years of age	Guidance is given in section section 4.2 “Posology and method of administration” of the SmPC informs about no available data in the paediatric population.	None
Use in patients aged 65 years and older*	Guidance is given in section 4.2 “Posology and method of administration” informs about the availability of limited data on the use of orlistat in the elderly.	None.

* this risk is contained only in the RMP for the 60 mg reference product

5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the BMI, a person’s weight (in kg) divided by the square of his or her height (in m). A person with a BMI of ≥ 30 is generally considered obese. A person with a BMI ≥ 25 is considered overweight. Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings. Worldwide obesity has nearly doubled since 1980. In 2008, more than 1.4 billion adults, 20 and older, were overweight. Of these, over 200 million men and nearly 300 million women were obese. 35% of adults aged 20 and over were overweight in 2008, and 11% were obese. 65% of the world's population live in countries where overweight and obesity kills more people than underweight. (WHO, Fact sheet N 311) In many countries of the WHO European Region the prevalence of obesity has tripled since the 1980s and the numbers of those affected continue to rise at an alarming rate (WHO, Obesity 2013). According to country estimates for 2008, over 50% of both men and women in the WHO European Region were overweight, and roughly 23% of women and 20% of men were obese. Based on the latest estimates in European Union countries, overweight affects 30-70% and obesity affects 10-30% of adults. (WHO, Obesity – Facts and figures 2013)

Overweight and obesity are major risk factors for a number of non-communicable chronic diseases such as cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2008, diabetes, musculoskeletal disorders (especially osteoarthritis - a highly disabling degenerative disease of the joints), and some cancers (endometrial, breast, and colon). The risk for these non-communicable diseases increases with the increase in BMI. (WHO, Fact sheet N 311) The risk of developing more than one of these diseases (co-morbidity) also increases with increasing body weight. Obesity is already responsible for 2–8% of health costs and 10–13% of deaths in different parts of the WHO European Region. (WHO, Obesity 2013)

5.2.2 Part VI.2.2 Summary of treatment benefits

Overweight and obesity, as well as their related non-communicable diseases, are largely preventable. Supportive environments and communities are fundamental in shaping people’s choices, making the healthier choice of foods and regular physical activity the easiest choice (accessible, available and affordable), and therefore preventing obesity.

Overweight and obesity can be reduced. At the individual level, people can limit energy intake from total fats and sugars, increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts, engage in regular physical activity (150 minutes per week for adults). (WHO, Fact sheet N 311) Participation in 150 minutes of moderate physical activity each week (or equivalent) is estimated to

reduce the risk of ischaemic heart disease by approximately 30%, the risk of diabetes by 27%, and the risk of breast and colon cancer by 21–25%. Physical activity also lowers the risk of stroke, hypertension and depression. (WHO, Obesity – Facts and figures 2013) At the societal level it is important to support individuals in following the recommendations above, through sustained political commitment and the collaboration of many public and private stakeholders and to make regular physical activity and healthier dietary choices available, affordable and easily accessible to all - especially the poorest individuals. The food industry can play a significant role in promoting healthy diets by reducing the fat, sugar and salt content of processed foods, ensuring that healthy and nutritious choices are available and affordable to all consumers, practicing responsible marketing especially those aimed at children and teenagers, ensuring the availability of healthy food choices and supporting regular physical activity practice in the workplace. (WHO, Fact sheet N 311)

Indications for treatment of overweight/obese patients are a BMI ≥ 30 or overweight with a BMI between 25 and 29.9 and concurrent presence of health disorders due to overweight (e.g. hypertension, type 2 diabetes) or abdominal fat-distribution pattern or diseases which aggravated by obesity or a high degree of psychosocial pressure. The basic therapy program should comprise dietetic, exercise and behaviour therapy. An additional drug therapy can be indicated in patients with a BMI ≥ 30 who had no sufficient success with the basic program and in patients with a BMI ≥ 27 with additional serious risk factors and/or comorbidities and in whom the basic therapy was not successful. Examples for drugs with weight reducing potential are sibutramine (selective serotonin and noradrenalin reuptake inhibitor), orlistat (inhibitor of gastrointestinal lipases) and rimonabant (CB1 receptor antagonist). Surgery can be indicated when the conservative treatment failed in patients with BMI ≥ 40 and in patients with BMI ≥ 35 with significant comorbidities, e.g. type 2 diabetes mellitus. (DAG, DDG, DGE, DGEM, 2007)

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The effect of orlistat in individuals with hepatic and/or renal impairment has not been studied. However, as orlistat is minimally absorbed, no dose adjustment is necessary in individuals with hepatic and/or renal impairment. For orlistat, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Orlistat is contraindicated in pregnancy. As it is not known whether orlistat is secreted into human milk, the use of orlistat is contraindicated during breast-feeding. The safety and efficacy of orlistat has not been established.

There are limited data about the use of orlistat in patients aged 65 and above. There are no data for the use of Orlistat in paediatric patients.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 5-1 Important identified risks

Risk	What is known	Preventability
Events of the digestive tract (Gastrointestinal events)	Orlistat might cause abdominal pain/discomfort, oily spotting from the rectum, passing of gas with discharge, faecal urgency, fatty/oily stool, excess passing of gas, liquid stools, oily evacuation and increased bowel movement very commonly (≥1/10) and rectal pain/discomfort, soft stools, inability to control bowel movements, swelling or feeling of fullness and tightness in the belly, tooth disorder and gum disorder commonly (≥1/100, <1/10).	The possibility of experiencing digestive tract adverse reactions may increase when orlistat is taken with a diet high in fat (e.g. in a 2000 kcal/day diet, > 30% of calories from fat equates to > 67 g of fat). The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. It is recommended that the diet should be rich in fruit and vegetables. The daily intake of fat, carbohydrate and protein should be distributed over three main meals.
Allergic reactions (hypersensitivity events)	Hypersensitivity reactions including severe allergic reactions, difficulties in breathing, swellings, itching, rash, and Skin blisters have been reported for orlistat. The frequency of occurrence is not known.	Orlistat should not be used in patients with known hypersensitivity to the active substance or to any of the excipients. If an allergic reaction occurs the patient should stop taking orlistat and seek for medical help immediately.
Events related to liver and bile tract including inflammation (Hepatobiliary events)	Orlistat might cause increase in liver enzymes and might cause gallstones.	Patients developing events related to liver and bile tract must seek medical evaluation immediately when signs and symptoms become serious. Orlistat must not be used in patients with disturbances of the bile flow.
Effect on blood clotting parameters (effect on coagulation parameters)	Decreased blood clotting parameters including prothrombin and increased INR have been reported for orlistat. The frequency of occurrence is not known.	Orlistat should not be used in patients treated with medicines which have an impact on blood clotting such as warfarin or other oral anticoagulants. Patients should inform their physician accordingly. Blood clotting parameters should be monitored in patients treated with concomitant oral drugs which prevent blood clots.

Risk	What is known	Preventability
Low blood glucose (hypoglycemia)	Weight loss may be accompanied by improved metabolic control in diabetes, but also may result in too low blood glucose.	Patients who are taking a medicinal product for diabetes should consult a doctor before starting treatment with orlistat, in case it is necessary to adjust the dose of the antidiabetic medicinal product.
Inflammation of the pancreas (pancreatitis)	Pancreatitis has been reported for orlistat. The frequency of occurrence is not known.	Patients are informed about symptoms of pancreatitis including severe abdominal pain sometimes radiating towards the back, possibly with fever, nausea and vomiting. If aforementioned symptoms occur the patient should stop taking orlistat and seek for medical help immediately.
Kidney disease induced by oxalate(oxalate nephropathy)	Orlistat might cause excessive urinary excretion of oxalate and a kidney disease induced by oxalate in patients. Oxalate nephropathy has been reported for orlistat. The frequency of occurrence is not known.	Patients developing oxalate nephropathy must seek medical evaluation immediately when signs and symptoms become serious.
Reduced function of the thyroid (hypothyroidism, reduced control of hypothyroidism)	Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered.	Patients taking levothyroxine should consult a doctor before starting treatment with orlistat, as orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted.
Convulsions, reduced control of epilepsy	Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic medicinal products. Orlistat may decrease the absorption of antiepileptic medicinal products, leading to convulsions	Patients taking an antiepileptic medicinal product should consult a doctor before starting treatment with orlistat, as they should be monitored for possible changes in the frequency and severity of convulsions. If this occurs, consideration could be given to administering orlistat and antiepileptic medicinal products at different times.

Risk	What is known	Preventability
Drug-drug interactions with ciclosporin (drug-drug interactions with ciclosporin)	A decrease in ciclosporin blood plasma levels has been observed when orlistat was administered concomitantly. This can lead to a decreased ciclosporin effect in reduction of the immune function of the body.	The combination of orlistat and ciclosporin is not recommended. However, if such concomitant use is unavoidable, more frequent monitoring of ciclosporin blood levels should be performed both after addition of orlistat and upon discontinuation of orlistat in ciclosporin treated patients. Ciclosporin blood levels should be monitored until stabilised.
Drug-drug interactions with acarbose (drug-drug interactions with acarbose)	No studies on interaction between orlistat and acarbose are available.	It is not recommended to use orlistat by patients receiving acarbose.
Drug-drug interactions with amiodarone (drug-drug interactions with amiodarone)	A slight decrease in blood plasma levels of amiodarone has been observed in patients who received orlistat concomitantly. The clinical relevance of this effect remains unknown.	In patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring (recording the electrical activity of the heart) is warranted.
Interaction with fat soluble vitamins (interaction with fat soluble vitamins)	Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K). The vast majority of patients receiving up to four full years of treatment with orlistat in clinical studies had vitamin A, D, E and K and beta-carotene levels that stayed within normal range.	In order to ensure adequate nutrition, patients on a weight control diet should be advised to have a diet rich in fruit and vegetables and use of a multivitamin supplement could be considered. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of orlistat or at bedtime.
Drug-drug interaction with drugs acting against HIV (drug-drug interactions with antiretrovirals)*	Orlistat may potentially reduce the absorption of medicines acting against HIV and could negatively affect the efficacy of those medications for HIV.	Patients should consult a physician before taking orlistat concomitantly with antiretroviral medications. Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV.

Table 5-2 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Impact on pregnancy prevention (impact on pregnancy prevention)	Orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some individual cases. The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhea.

Risk	What is known (Including reason why it is considered a potential risk)
Use of Orlistat in patients with body mass index (BMI) < 28 kg/m^2 which is a not approved patient group (Inappropriate / off-label use in patients with BMI <28kg/m^2)*	There is a potential for off-label use of orlistat in patients with BMI < 28 kg/m^2. Adverse event reports supported the conclusion that the frequency of this off-label use is small and the adverse events that have been reported in the inappropriate patient populations followed the known safety profile of the product, i.e., the vast majority were digestive tract related, and have not resulted in any serious consequences.
Inflammation of small blood vessels which affects skin, joints, bowel or kidney (Henoch-Schonlein purpura)*	It needs to be further evaluated if orlistat may cause Henoch-Schonlein purpura. Patients developing Henoch-Schonlein purpura must seek medical evaluation immediately when signs and symptoms become serious.
Use in patients with eating disorders*	Before starting the treatment with orlistat, the physician needs to evaluate if the patient suffers from any eating disorder.
Drug-drug interactions with oral anticoagulants (drug-drug interactions with oral anticoagulants)	Decreased blood clotting parameters including prothrombin and increased INR have been reported for orlistat. The frequency of occurrence is not known. Orlistat should not be used in patients treated with warfarin or other oral anticoagulants.
Drug-drug interactions with antiepileptic drugs (drug-drug interactions with antiepileptic drugs)	Orlistat may decrease the absorption of antiepileptic medicinal products, leading to convulsions.
Drug-drug interactions with levothyroxine / iodine salts (drug-drug interactions with levothyroxine / iodine salts)	Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of iodine salts and/or levothyroxine..
Drug-drug interactions with antidepressant and antipsychotic drugs (drug-drug interactions with antidepressant and antipsychotic drugs)	No data are available

* this risk is contained only in the RMP for the 60 mg reference product

Table 5-3 Missing information

Risk	What is known
Use in patients with hepatic impairment (Use in patients with impaired liver function)	The effect of orlistat in individuals with hepatic impairment has not been studied. However, as orlistat is minimally absorbed, no dose adjustment is necessary in individuals with hepatic impairment.
Use in patients with renal impairment (Use in patients with impaired kidney function)	The effect of orlistat in individuals with renal impairment has not been studied. However, as orlistat is minimally absorbed, no dose adjustment is necessary in individuals with renal impairment.
Use during pregnancy	For orlistat no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Orlistat should not be used if the patient is pregnant.
Use during lactation	It is not known whether orlistat is secreted into human milk. Orlistat should not be used if the patient is breast-feeding.
Use in children < 12 years of age	The safety and efficacy of in children has not been established. No data on safety and efficacy are available.
Use in patients aged 65 years and older*	There are limited data on the use of orlistat in the elderly. However, as orlistat is minimally absorbed, no dose adjustment is necessary in the elderly.

* this risk is contained only in the RMP for the 60 mg reference product

5.2.5 Part VI.2.5 Summary of additional risk minimization 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 minimizing 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 minimization measures. This medicine has no additional risk minimization measures.

5.2.6 Part VI.2.6 Planned post authorization development plan

None.

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

Version	Date	Safety Concerns	Comment
2.0	21 May 2013	- N/A - Identified risk rectal bleeding - Identified risk cholelithiasis	- New template - related to identified risk gastrointestinal events - related to identified risk hepatobiliary events

Version	Date	Safety Concerns	Comment
		- hepatobiliary events including cholelithiasis, hyperoxaluria/oxalate nephropathy, rectal bleeding, pancreatitis, hypothyroidism and other thyroid disorders due to interaction between orlistat and levothyroxine, interaction with ciclosporin, amiodarone, anticoagulants, fat soluble vitamins, oral contraceptives, off-label use in patients with BMI < 28 kg/m^2, off-label use in children and adolescents under 18 years old, use in patients with eating disorders, convulsions due to interaction between orlistat and antiepileptic agents and severe liver injury	- Addition of "… or any time schedule proposed by HA, with PSURs" to the PhV measure "Scheduled cumulative reviews of spontaneous adverse event reports at 6, 12 and 24 months (as line listing)."
		- potential risk "Off-label use in patients with BMI < 28 kg/m^2"	- On the basis of 5 case reports involving an off-label use of orlistat in patients with BMI < 28 kg/m^2 (of 23 cases altogether in the reviewed time period) upgrading to an identified risk.
		- rectal bleeding, hepatobiliary events including cholelithiasis, hyperoxaluria/oxalate nephropathy, interaction with anticoagulants, off-label use in patients with BMI < 28 kg/m^2, severe liver injury, pancreatitis and off-label use in children and adolescents under 18 years old	- Addition of already available educational material information into the RMP. Inclusion of the updated Educational material for prescription and non-prescription orlistat into the RMP – Annex 11.
3.0	… Apr 2015		Following Final PRAC PSUR assessment report within EMEA/H/C/PSUSA/00002220/2014 02 from 11 Sep 2014, the following was changed / amended in the RMP and elaborated throughout the RMP:
		Important identified risk : Hyperoxaluria / Oxalate nephropathy	"Renal insufficiency" added to this risk
		Interaction with HAART (Highly Active Antiretroviral Therapy)	Added as important identified risk
		Interaction with human carboxylesterase (CES) substrates / interaction through inhibition of ester hydrolysis, Interaction with benzodiazepines, malignancies	Added as important potential risks

Version	Date	Safety Concerns	Comment
		Use during pregnancy Interaction with antidepressants and antipsychotics (including lithium), Lichenoid keratosis, Vasculitis, Abuse	Added as missing information On the basis of Sandoz PSUR 3 for Orlistat containing products, dated 27 Mar 2015, the following risks were added to the RMP and elaborated throughout the RMP: Added as important potential risks Additionally, - Part II, Module V was deleted from the RMP as this is not needed for a generic RMP following the current EU RMP legislation. - the lay language in Part VI was re-worked completely. - all chapters and headers of the RMP were adapted to the currently valid EU RMP template. - "Important" was related from all places describing missing information. - a typo was corrected in the educational material: in the overview tables of the energy content of main nutrients the energy content of fat was corrected from 1 g = 9 kcal (30 kJ) to 1 g = 9 kcal (39 kJ) - the marketing status (Annex 3) was updated and SPCs and PLs included in Annex 2.
3.1	23 Dec 2015	<u>Important identified risk:</u> – Gastrointestinal events including rectal bleeding: – Hypersensitivity events: – Hepatobiliary events including cholelithiasis: – Effect on coagulation parameters	Following the PRAR for renewal NL/H/3408001/R/001, and NL/H/3409/001/R/001, the following was changed / amended in the RMP and elaborated throughout the RMP: Deletion of "…including rectal bleeding" Added Deletion of "…including cholelithiasis" Added

Version	Date	Safety Concerns	Comment
		– Hypoglycemia	Added
		– Pancreatitis	Changed from category Important potential risks
		– Hyperoxaluria / Oxalate nephropathy / Renal insufficiency)	Deletion of “Hyperoxaluria / …/ Renal insufficiency”
		– Hypothyroidism, reduced control of hypothyroidism	Added / modified
		– Convulsions, reduced control of epilepsy	Added / modified
		– Drug-drug interactions with ciclosporin	Wording modified
		– Drug-drug interactions with acarbose	Wording modified
		– <u>Drug-drug interactions with amiodarone</u>	Wording modified
		<u>Important potential risks:</u>	
		– Impact on pregnancy prevention	Added
		– Drug-drug interactions with oral anticoagulants	Wording modified
		– Drug-drug interactions with antiepileptic drugs	Wording modified
		– Drug-drug interactions with levothyroxine / iodine salts	Wording modified
		– Drug-drug interactions with antidepressant and antipsychotic drugs	Wording modified
		<u>Missing information:</u>	
		– Use in patients with hepatic impairment	Added
		– Use in patients with renal impairment	Added
		– Use during pregnancy	Changed from category Important potential risks
		– Use during lactation	Added
		– Use in children < 12 years of age	Added

Version	Date	Safety Concerns	Comment
		– Interaction with HAART (Highly Active Antiretroviral Therapy) – Off-label use in patients with BMI < 28 kg/m2 – Interaction with human carboxylesterase (CES) substrates / Interaction through inhibition of ester hydrolysis – Severe liver injury – Lichenoid keratosis – Vasculitis – Malignancies – Off-label use in children and adolescents under 18 years old – Abuse – Use in patients with eating disorders – Diversion from care – Limited experience in non-prescription environment – Use in subjects aged 65 and above	All deleted
		Additional risk minimization (e.g. educational material for patients)	Deleted
3.2	18 Apr 2016	-N/A	Changes were made in the course of FRAR NL/H/3409/001/R/001 dated 24 Mar 2016. The following was changed / amended in the RMP and elaborated throughout the RMP. Part I: Product(s) overview was updated
		Important identified risks: – Drug-drug interaction with antiretrovirals	Added
		Important potential risks: – Inappropriate / off-label use in patients with BMI < 28 kg/m^2 – Henoch-Schonlein purpura – Use in patients with eating disorders	All added

Version	Date	Safety Concerns	Comment
		Missing information: – Use in patients aged 65 years and older N/A N/A	Added Annex 2:updated versions of SmPC and PIL were included Annex 3: Worldwide marketing status by country was updated
3.3	22 Apr 2016	 -N/A Important identified risks: – Drug-drug interaction with antiretrovirals Important potential risks: – Inappropriate / off-label use in patients with BMI < 28 kg/m^2 – Henoch-Schonlein purpura – Use in patients with eating disorders Missing information: – Use in patients aged 65 years and older	Changes were made in the course of FRAR NL/H/3409/001/R/001 dated 24 Mar 2016 revision where RMS requested to separate strength specific sections. Part I: Product(s) overview was updated Indicated with * this risk is contained only in the RMP for the 60 mg reference product Indicated with * this risk is contained only in the RMP for the 60 mg reference product Indicated with * this risk is contained only in the RMP for the 60 mg reference product