NOVARTIS

Chief Medical Office & Patient Safety

Vildagliptin/Vildagliptin-Metformin

LAF237/LMF237

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Vildagliptin/Vildagliptin-Metformin
Product(s) concerned (brand name(s)):	Galvus®/Jalra®/Xiliarx®/Eucreas®/Icandra®/Zomarist
Document status:	Final
Version number:	15.2
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Date of final sign off	07-Jul-2021

Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP: The current RMP version (v15.2) is updated based on recommendations from the PRAC during the procedure (EMEA/H/C/WS1970).

The EMA has recommended to remove "Pancreatic cancer" as important potential risk from the list of safety risks in the assessment of the EU RMP (v15.1). The rationale for the removal of this risk has been provided in Section 8.2 of the RMP.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 15.1
Part I	Indication updated to align with recently approved Galvus/Eucreas SmPC and its clones.
Part II	SI: No change SII: No change SIII: No change SIV: No change SV: No change SVI: No change SVII: Updated the safety concerns list with risk in relevant subsections. The important potential risk "Pancreatic cancer" has been removed. SVIII: Updated the summary of safety concerns list in Table 9-1 with removal of "Pancreatic cancer" as an important potential risk.
Part III	Updated the section with removal of "Pancreatic cancer" as an important potential risk and removal of "Malignancy and Neoplasm" from the list of specific adverse reaction targeted follow-up checklist.
Part IV	No change
Part V	Updated the risk minimization measures to align with the list of safety concerns, specifically the removal of "Pancreatic cancer" as an important potential risk in Table 12-1 and Table 12-2.
Part VI	Updated this section to align with the list of safety concerns, specifically the removal of "Pancreatic cancer" as an important potential risk and updated indication and dosing information to align with the recently approved Galvus/Eucreas SmPC and its clone.
Part VII	Annex 1: No change Annex 2: No change Annex 3: No change Annex 4: Targeted follow-up checklist for "Malignancy and Neoplasm" removed. Annex 5: No change Annex 6: No change Annex 7: References related to pancreatic cancer have been removed.

Part	Major changes compared to RMP v 15.1
	Annex 8: Updated to reflect the changes made to the current RMP

Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within procedure number
V15.0	27-Oct-2020	EMEA/H/C/WS1970
V15.1	07-Mar-2021	EMEA/H/C/WS1970

Details of the currently approved RMP:

Version number: 14.1

Approved with procedure: EMEA/H/C/xxxx/WS/1088

Date of approval (opinion date): 21-Apr-2017

QPPV name: Dr. David Lewis

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ADRs	Adverse Drug Reactions
AEs	Adverse Events
ALT	Alanine Transaminase
AP	Acute Pancreatitis
ARB	Angiotensin Receptor Blocker
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical Classification
bid	Twice a day
BMI	Body Mass Index
C_{max}	Maximum Concentration
CHF	Congestive Heart Failure
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DA	Disease Analyzer
DDD	Defined Daily Dose
DILI	Drug Induced Liver Injury
DPP-4	Dipeptidyl-Peptidase IV
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FDC	Fixed-Dose Combination
GFR	Glomerular filtration rate
GLP-1	Glucagon-like Peptide 1
GI	Gastrointestinal
GIP	Glucose-dependent Insulinotropic Peptide
GPRD	General Practice Research Database
GVP	Good pharmacovigilance practice
HbA_{1c}	Glycated hemoglobin (hemoglobin A1c)
HIV	Human Immunodeficiency Virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA reductase
INN	International Nonproprietary Names
IR	Incidence Rate
IRR	Incidence Rate Ratio
LFTs	Liver function tests
MAH	Marketing Authorization Holder
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NHANES	National Health and Nutrition Examination Survey

NYHA	New York Heart Association
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MONICA	Monitoring Trends and Determinants on Cardiovascular Diseases
OPED	Odense PharmacoEpidemiologic Database
OR	Odds Ratio
PASS	Post-authorization Safety Study
PV	Pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient Treatment Year
PV	Pharmacovigilance
PY	Person-Year
qd	Once daily
QPPV	Qualified person responsible for pharmacovigilance
RMM	Risk Minimization Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SU	Sulfonylurea
SYE	Subject Year of Exposure
TIA	Transient Ischemic Attack
T2DM	Type 2 Diabetes Mellitus
TZD	Thiazolidinedione
ULN	Upper limit of normal
US	United States

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview (Galvus)

Active substances (INN or common name)	Vildagliptin
Pharmacotherapeutic group (ATC Code)	A10BH02 Vildagliptin
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Galvus, Jalra, Xiliarx
Marketing authorization procedure	Centralized Procedure
Brief description of the product	Chemical class: The active substance of Galvus, vildagliptin, is the S-enantiomer of a 2-cyano-pyrrolidide and belongs to the DPP 4 inhibitor class.
	Summary of mode of action: Dipeptidyl peptidase IV (DPP-4) is an enzyme responsible for the degradation and inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which plays a critical role in glucose homeostasis.
	Important information about its composition: Galvus is available as 50 mg tablet and contain Lactose, anhydrous, microcrystalline cellulose, sodium starch glycolate (type A) and magnesium stearate as excipients
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	Current: Vildagliptin is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus: • as monotherapy in patients in whom metformin is inappropriate due to contraindications or intolerance. • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 of currently approved Galvus/Eucreas SmPC and its clone for available data on different combinations).
	Proposed (if applicable): None
Dosage in the EEA	Current: In adults, when used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.
	Proposed (if applicable): None.

Pharmaceutical form and strengths	Current: Tablets, 50 mg
	Proposed (if applicable): None.
Is/will the product be subject to additional monitoring in the EU?	No

Table 1-2 Part 1.2 Product Overview (Eucreas)

Active substances (INN or common name)	Vildagliptin and metformin hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	A10BD08-metformin and vildagliptin
Marketing Authorization <Holder> <Applicant>	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Eucreas, Icandra, Zomarist
Marketing authorization procedure	Centralized Procedure.
Brief description of the product	Chemical class: Oral antidiabetic drug Eucreas® combines two antidiabetic compounds: vildagliptin and metformin. Vildagliptin is the S-enantiomer of a 2-cyano-pyrrolidide and a member of the dipeptidyl peptidase IV (DPP-4) inhibitor drug class, and metformin is a member of the biguanide class of anti-diabetic drugs.
	Summary of mode of action: DPP-4 is an enzyme responsible for the degradation and inactivation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which plays a critical role in glucose homeostasis. Metformin has effects that are complementary to the actions of vildagliptin, including reduction in hepatic glucose production and increased insulin sensitivity.
	Important information about its composition: Eucreas is available as 50 mg/850 mg and 50 mg/1000 mg film-coated tablets with hydroxypropylcellulose and magnesium stearate as tablet core and hypromellose, titanium dioxide (E 171), Iron oxide, yellow (E 172), macrogol 4000 and Talc as film-coating.
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	Eucreas is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus: • in patients who are inadequately controlled with metformin hydrochloride alone. • in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide

	adequate glycaemic control (see sections 4.4, 4.5 and 5.1 of currently approved Galvus/Eucreas SmPC and its clone for available data on different combinations).
	Proposed (if applicable): None
Dosage in the EEA	Current: Recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.
	Proposed (if applicable): None.
Pharmaceutical form and strengths	Current: Film-coated tablets of 50mg/850mg and 50mg/1000mg (vildagliptin/metformin).
	Proposed (if applicable): None.
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Type 2 diabetes mellitus

Incidence:

Several epidemiological studies assessed the incidence of T2DM in Europe (e.g. Vazquez et al 2000, Meisinger et al 2002, Bonora et al 2004, Brauchli et al 2008, Joseph et al 2010) or in the US (Burke et al 1999, Fox et al 2006, Geiss et al 2006, Nguyen et al 2012). These studies show a wide range of incidence rate (IR) or annual/cumulative incidence estimates ranging approximately from 1 to 17/1,000 (person-years [PY]), depending on various factors, such as the age and sex distribution of the studied population, and on the prevalence and distribution of other relevant risk factors for development of T2DM, such as body mass index (BMI), hypertension, cardiovascular disease, region/country, race/ethnicity, or life style factors (e.g. diet, exercise, alcohol). Generally, the T2DM incidence increases with age and is generally slightly higher in men than women. The IRs peak around the age of 60-69 years in men and 70-79 years in women.

A recent systematic review of 47 studies reporting trends in the incidence of diabetes among adults has shown that in 2006-14 increasing incidence trends were reported in 33% of populations, whereas 30%, and 36% had stable or declining incidence, respectively (Magliano et al 2019).

Prevalence

The International Diabetes Federation (2019), estimated that in 2019, 463.0 million adults aged 20-79 years of age have diabetes worldwide (9.3% of the population of that age group), with 240.1 (51.9%) million being males. It is estimated that 79.4% of these live in low- and middle-income countries. Based on the 2019 estimates, this global prevalence number is projected to

reach 578.4 million (10.2%) by 2030, and 700.2 million (10.9%) by 2045. The prevalence is lowest among adults aged 20-24 years (1.4% in 2019). Among adults aged 75-79 years the diabetes prevalence is estimated to be 19.9% in 2019, and predicted to rise to 20.4% and 20.5% in 2030, and 2045, respectively. Out of the 463.0 million adults living with diabetes, an estimated 231.9 million (50.1%) individuals have undiagnosed diabetes (overwhelmingly T2DM).

In Europe, the diabetes raw prevalence is estimated at 8.9% (6.3% for the age-adjusted comparative prevalence) corresponding to an estimated 59.3 million adults. Germany has the highest number of adults with diabetes 9.5 million (15.3%), followed by the Russian Federation with 8.3 million (7.8%), Turkey with 6.6 million (12.0%), Italy with 3.7 million (8.3%), Spain with 3.6 million (10.5%), France with 3.5 million (7.6%), Poland with 2.3 million (8.1%), and the UK with 2.7 million (5.6%).

For the US, the number of adult people with diabetes is estimated to be 31.0 million, corresponding to 13.3% of the adult population. Corresponding data for Canada estimate 2.8 million adults with diabetes (10.1%).

China has the highest number of people with diabetes worldwide (116.4 million), with a prevalence of 10.9%, followed by India with 77.0 million (8.9%).

The Western Pacific region has the highest number of patients with diabetes (162.6 million [9.6%]). North America and the Caribbean is the region with the highest raw prevalence of diabetes (13.3%), while Africa has the lowest prevalence (3.9%), but is expected to have an increase of the prevalence of 143% by 2045.

Diabetes caused at least 760.3 billion US$ in health expenditure globally in 2019 (International Diabetes Federation 2019).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Demographics

T2DM accounts for 90 to 97% of diabetes worldwide (Amos et al 1997, Oldroyd et al 2005, International Diabetes Federation 2019). It is most commonly diagnosed in persons > 40 years of age, although younger people are now presenting with T2DM more frequently, due to the rapid rise in obesity (Singh et al 2004, Hannon et al 2005). The prevalence is generally slightly higher in men than women, however, it can be higher in elderly women (> 70 years of age) compared to men of the same age group. In 2019, 463.0 million people have been estimated to have diabetes; by 2045 this number will have risen by over 50% (International Diabetes Federation 2019). Much of this increase will occur in developing countries, due to population growth, aging, unhealthy diets, obesity and sedentary lifestyles.

In European countries, the age-specific prevalence of diabetes is ≤ 10% in subjects < 60 years and between 10 and 20% at 60 to 79 years of age.

More detailed age- and gender-stratified data from European countries (Table 2-1) as well as from the US (Table 2-2) are provided below.

Table 2-1 Detailed age- and sex-stratified prevalence (%) of diagnosed and undiagnosed diabetes in men and women from various European countries

Country	Age (years)	Men	Women
Sweden 1994 (MONICA)	30-39	1.8	1.0
	40-49	5.3	4.4
	50-59	4.5	6.1
	60-69	13.9	14.3
	70-74	16.7	13.1
Finland (MONICA)	40-49	4.7	3.8
	50-59	9.6	6.0
	60-64	9.2	7.8
Finland (Oulu)	70-79	36.9	34.3
	80-89	10.7	54.6
Netherlands (Hoom)	50-59	8.0	4.4
	60-69	10.7	12.5
	70-77	16.0	19.7
UK (Newcastle)	30-39	0	0
	40-49	9.7	3.7
	50-59	13.6	8.0
	60-69	17.1	13.9
	70-76	16.4	12.0
Italy (Cremona)	40-49	4.1	2.1
	50-59	8.2	5.0
	60-69	18.2	13.0
	70-79	17.1	20.6
	80-89	15.2	34.9
Spain (Catalonia)	30-39	3.5	1.3
	40-49	4.6	4.8
	50-59	11.3	9.0
	60-69	18.6	25.3
	70-79	19.6	30.9
	80-89	21.7	24.7

MONICA = Monitoring Trends and Determinants on Cardiovascular Diseases

Source: DECODE Study Group (2003)

Table 2-2 Standardized prevalence data of diagnosed and undiagnosed diabetes from US NHANES data among adults 20 years or older by gender and age

Characteristic	Prevalence (%)
Sex	
Women	8.2
Men	10.6
Age (years)	
20-39	2.4
40-59	9.8

Characteristic	Prevalence (%)
≥ 60	21.1
≥ 65	21.8

NHANES = National Health and Nutrition Examination Survey
Source: Cowie et al (2006)

Crude prevalence data for diagnosed and undiagnosed diabetes from the US National Health and Nutrition Examination Survey (NHANES) by race/ethnicity among adults 20 years of age or older are displayed in the table below.

Table 2-3 Crude prevalence data for diagnosed and undiagnosed diabetes from US NHANES data by race/ethnicity among adults 20 years or older

Race/Ethnicity	Crude prevalence (%)
Non-hispanic white	30.5
Non-hispanic black	28.1
Hispanic	28.6
Non-hispanic Asian	10.1
Non-hispanic other	2.7

Source: Cheng et al (2019)

Risk factors for the disease

The most relevant risk factors for T2DM include (American Diabetes Association 2014):

- Age > 45 years
- African-American, Hispanic, Asian, Pacific Islander, or Native-American ethnicity
- Overweight (BMI ≥25 kg/m^2), especially abdominal obesity, or other clinical conditions associated with insulin resistance (e.g., acanthosis nigricans)
- First-degree relative with T2DM
- History of gestational diabetes or delivery of infant weighing ≥4 kg
- Polycystic ovary syndrome
- History of cardiovascular disease (CVD)
- Hypertension (≥140/90 mmHg or on therapy for hypertension), dyslipidemia (High-Density Lipoprotein (HDL) cholesterol level < 35 mg/dl [0.90 mmol/l] and/or a triglyceride level >250 mg/dl [2.82 mmol/l]), or other metabolic syndrome features
- Glycated hemoglobin (HbA1c) ≥5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing
- Physical inactivity

The main existing treatment options

In addition to non-pharmacologic lifestyle modifications, such as increased physical activity, healthy diet, or obesity management (Wu et al 2014), various pharmacologic treatment options for T2DM are available and include the below listed anti-diabetic drugs/drug classes (Mazzola 2012, Tsoutsouki et al 2020):

- DPP-4 inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)
- Biguanides (i.e. metformin)

- Sulfonylureas (e.g. glibenclamide, glimepiride, glipizide, glyburide)
- Thiazolidinediones (e.g. pioglitazone, rosiglitazone)
- Glinides (nateglinide, repaglinide)
- α-glucosidase inhibitors (e.g. acarbose, miglitol)
- Glucagon-like peptide 1-receptor agonists (GLP-1 RA) (e.g. exenatide, liraglutide)
- Amylin agonists (e.g. pramlintide)
- Insulin
- Sodium/glucose cotransporter 2 (SGLT-2) inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin)

Natural history of type 2 diabetes mellitus, including morbidity and mortality

Morbidity:

T2DM, if not well controlled, may cause various forms of both short- and long-term complications. These include macrovascular diseases (hypertension, hyperlipidemia, cardiovascular disease, coronary artery disease including, myocardial infarction, cerebrovascular disease including stroke, peripheral vascular disease), microvascular diseases (diabetic retinopathy [may result in blindness], diabetic nephropathy [may result in kidney failure], diabetic neuropathy, and diabetic foot complications [may result in lower limb amputation]), as well as various forms of cancers, especially, in T2DM patients with high BMI (e.g., intrahepatic cholangiocarcinoma, bladder cancer, colorectal cancer, kidney cancer, breast cancer, endometrial cancer) (Wu et al 2014, World Health Organization 2016, International Diabetes Federation 2019).

Cardiovascular disease: CVD is a primary cause of morbidity and mortality in both prediabetes and T2DM (Wu et al 2014). Elevated levels of blood glucose, and diabetes itself, lead to increased risk of CVD through multiple mechanisms, including insulin resistance, inflammation, endothelial dysfunction, and the toxic effects of glucose on microvasculature. In addition, elevated blood glucose levels are associated with a common set of other underlying metabolic risk factors, including hypertension, dyslipidemia, and central obesity. The risk is also strongly affected by smoking and by low levels of physical activity. The prevalence of coronary artery disease is estimated at approximately 21%, that of any CVD at 32% in adults with diabetes living in high- and middle income countries (International Diabetes Federation 2019).

Diabetic retinopathy (DR): DR is the leading cause of vision loss in adults aged 20-74 years. One third of T2DM patients have signs of DR, and many of these are afflicted with vision-threatening diabetic retinopathy (VTRD), defined as severe non-proliferative DR or proliferative DR (PDR), or the presence of diabetic macular edema (DME), the major cause of vision loss in T2DM. Prevalence and risk factors of DR have been studied, but epidemiological data on DME are relatively scarce. The prevalence of any DR and PDR in T2DM has been estimated at around 25% for any DR, and 3% for PDR, respectively. In general, T2DM patients in Western communities have a higher prevalence of DR than their Asian counterparts. In the US, studies estimate that 28.5-40.3% of T2DM patients have DR, and 4.4-8.2% of them have VTDR (Lee et al 2015).

Diabetic nephropathy: Diabetic nephropathy is one of the most important microvascular complications, whose earliest manifestation is the presence of minute amounts of urinary protein (microalbuminuria) (Wu et al 2014). Chronic kidney disease (CKD) in people with diabetes can result from diabetic nephropathy or can be the result of other associated conditions such as hypertension, polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections, or macrovascular angiopathy. The proportion of end stage renal disease (ESRD) attributed to diabetes varies between 10% to 67%. The prevalence of ESRD is up to 10-times higher in people with diabetes than in those without (International Diabetes Federation 2019).

Diabetic neuropathy: Peripheral neuropathy is the most common form of diabetes-related neuropathy. It affects the distal nerves of the limbs, particularly those of the feet. It mainly alters the symmetrical sensory function causing abnormal feelings and progressive numbness. These conditions facilitate the development of ulcers resulting from external trauma and/or abnormal distribution of the internal bone pressure (the so-called 'diabetic foot'). The reported prevalence of diabetes-related peripheral neuropathy ranges from 16% to as much as 87% with painful diabetes-related neuropathy reported in about 26% of adults with diabetes (International Diabetes Federation 2019).

Diabetic foot disease: Damage to blood vessels and nerves (from vascular and neurological disease processes) often leads to ulceration and subsequent limb amputation. Diabetes accounts for 50% of non-traumatic amputation of the lower limb (Ulbrecht et al 2004). The global prevalence of diabetic foot complications varies between 3% in Oceania to 13% in North America, with a global average of 6.4%; prevalence is higher in men than women. Lower limb amputation is 10- to 20-times more common in people with diabetes compared to those without. It has been estimated that, globally, a lower limb (or part of a lower limb), is lost to amputation every 30 seconds as a consequence of diabetes (International Diabetes Federation 2019).

Mortality:

Approximately 4.2 million adults aged 20-79 years were estimated to die as a result of diabetes and its complications in 2019. This is equivalent to one death every eight seconds. Diabetes is estimated to be associated with 11.3% of global deaths from all causes among people in this age group. Almost half (46.2%) of deaths associated with diabetes among the 20-79 years age group are in people under the age of 60 years (International Diabetes Federation 2019).

T2DM mortality is in the range of approximately 20 to >110 per 1,000 PYs (e.g. Koskinen et al 1998, Gimeno et al 2002, Engelgau et al 2004, Mulnier et al 2006, Röckl et al 2017) with differences largely driven by different age and gender. Mortality increases with age and is higher in men than women.

Complications from CVD and cancer are the most common causes of death in patients with T2DM (Tseng 2004).

Important co-morbidities

Important co-morbidities in T2DM include risk factors for T2DM development, as well as short-/long-term complications from T2DM, see table below (also including the co-morbidity associated drug therapy)

Table 2-4 Co-morbidities and their associated drug therapies in patients with type 2 diabetes mellitus

Co-morbidity	Drug therapy
Hypertension	Antihypertensives (including ACEIs, ARBs, diuretics, beta-blockers, calcium channel blockers, etc.)
Cardiovascular disease, ischemic heart disease (angina, prior MI)	Aspirin, antiplatelet agents, nitrates, beta-blockers, calcium channel blockers, statins, antiplatelets
Stroke or TIA	Aspirin, antiplatelet agents
Peripheral vascular disease	
Dyslipidemia	Statins, fibrates, ezetimibe
Obesity	--
Nephropathy	ACEIs, ARBs, diuretics, statins
Retinopathy	Anti-VEGF drugs
Neuropathy	NSAIDs, acetaminophen, opioids, antidepressants, antiepileptic drugs
Cancer	Depending on cancer type, including various chemotherapeutic/cytotoxic agents, immunotherapy, targeted therapy, hormone therapy

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; MI = myocardial infarction; TIA = transient ischemic attack; VEGF = vascular endothelial growth factor, NSAIDs = Non-steroidal anti-inflammatory drugs

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicities	
Respiratory System: In rodents, increased accumulation of alveolar macrophage was observed. It was generally minimal in severity, did not increase in severity with longer duration of treatment and was not seen in the dogs.	The appearance of foamy macrophages represents an exaggerated pharmacological effect of DPP-4 inhibition in rats. The presence of good exposure margins at the no-effect level dose level in rats compared with human clinical exposure and the very minor nature of this finding indicate that it does not represent a risk to humans at the recommended clinical dose. This is confirmed by the lack of any vildagliptin-related respiratory findings in large-scale phase 3 human trials.
Gastrointestinal system: Gastrointestinal toxicity findings of vomiting, diarrhea, fecal blood were observed in dogs and the severity of these findings were dose dependent. Similar gastrointestinal findings were not observed in other animal species and considered as dog specific.	No vildagliptin-related gastrointestinal disorders were noted in large-scale human clinical trials and the findings from animal studies are considered as dog specific. Thus, this toxicological finding is not considered to represent a human safety risk in normal clinical use of vildagliptin.
Skin findings: Skin changes (blisters/skin flaking and necrotic lesions with correlating histopathological changes) occurred at all doses and were consistently located on the extremities (hands, feet, ears and tail) in monkeys. These changes were not reversible in the monkeys treated at 160 mg/kg/day that were evaluated following the 4-week recovery period. No treatment-related skin lesions of this nature were observed in any other toxicology species.	Skin lesions have not been reported in vildagliptin clinical program, either in patients or in healthy volunteers receiving up to 600 mg/day. Thus, these findings are not considered to indicate a risk to humans treated at the recommended clinical doses.
Symptoms of acute toxicity - Symptoms of acute toxicity in Cynomolgus monkeys include edema formation in distal extremities associated with skeletal muscle necrosis, elevations of (Lactate dehydrogenase) LDH, creatine kinase (CK), alanine transaminase (ALT) and aspartate transaminase (AST) in plasma, hypothermia, hypotension, tachycardia, morbidity, and death in few isolated instances. Symptoms are reversible in surviving animals even if treatment is continued - Cynomolgus monkeys originating from Mauritius appear especially sensitive to vildagliptin	Compared to humans, the Cynomolgus monkey appears to exhibit a unique response to DPP-4 inhibition, which can induce acute toxicity symptoms and affect skin and vascular reactivity at a macro- and microvascular level. In addition, data suggest that Cynomolgus monkeys originating from Mauritius are especially sensitive to vildagliptin. Similar toxicity has not been observed in other animal species such as mice, rats, or dogs. A comprehensive review of the clinical trial and post-marketing data has been performed focusing on events that could possibly be related to the acute symptoms observed in Cynomolgus

- Spontaneous death after a single dose was observed at 40 mg/kg and 160 mg/kg in Mauritius and Asian monkeys, respectively These observations had not been observed in the non-clinical studies performed in support of the original application although there are no differences in exposures to vildagliptin and its metabolites between the two study periods.	monkeys, including events of edema, muscle-related events, creatine phosphokinase (CPK) elevations, and death. The results reveal no indication of a specific pattern which could be considered of clinical relevance or relevance within the context of acute findings observed in monkeys. In conclusion, there is no evidence that humans are at risk of serious acute toxicity as seen in the monkeys.
General Safety Pharmacology	
Cardiovascular changes were observed in dogs and monkeys A dog telemetry study showed ECG changes consistent with inhibition of cardiac sodium channels. Small increases in heart rate and blood pressure, but no conduction changes, were also observed in a telemetry study in monkeys Cardiac conduction changes have been observed in repeated dose studies at high doses in dogs, and are believed to account for sudden death	There is an adequate safety margin for any cardiovascular effects in humans is provided by the lack of any treatment-related cardiovascular effects in a human study using continuous cardiac monitoring at the highest tolerated dose of 400 mg (4 times the maximum anticipated clinical dose), and by the lack of effects on cardiac conduction or cardiac events in large populations in phase 3 studies Cardiac conduction disturbances were further investigated in humans and the safety specification for conduction disturbances. The adverse event (AE) incidence rates of cardiac conduction disturbances were low and similar across all groups. The subject years of exposure (SYE)-adjusted serious adverse event (SAE) rates were similar on vildagliptin 50 mg bid and total comparators (0.06 and 0.05, respectively), and slightly higher on vildagliptin 50 mg qd (0.16). The discontinuation rate due to conduction disturbances on vildagliptin was very low and there were no discontinuations on placebo. Cardiac conduction defects have been reviewed per previous versions in Periodic Safety Update Report (PSUR). In Galvus PSUR 6 Novartis proposed that this risk has been adequately characterized and therefore to be removed from RMP and future PSURs. This proposal was accepted by European Medicines agency (EMA). Overall, these datasets do not indicate that a risk of conduction disturbances has been identified in humans.
Nervous system Neurologic findings (ataxia, impaired righting reflex, tremors, rigidity and dilated pupils) were observed in dogs at the highest dose used in these studies (75 mg/kg/day) with signs appearing 1-2 hours after dosing (corresponding with C_{max}), and where recovery was observed, declined by approximately 5 hours post dose. One animal treated at 60 mg/kg/day showed	Slight imbalances in dizziness and headache were seen in clinical trials, but no other imbalances were seen in the Nervous System SOC (System Organ Class). No imbalances were seen in the Psychiatric Disorders SOC.

severe ataxia, loss of righting reflex and recumbency, without accompanying tremors or rigidity. There were no observable effects on central nervous system (CNS) function/neurobehaviour at doses up to 75 mg/kg/day as observed via video feed in the 10-dog telemetry study for up to 4 hours post-dose.	
Carcinogenicity findings No vildagliptin-related carcinogenicity findings in the rats. Some findings observed in mice at high doses were - increased incidences of mammary adenocarcinoma and hemangiosarcoma at high doses only.	Mammary adenocarcinoma is likely the result of an effect on the pituitary-gonadal axis that (in common with many hormonal changes occurring in ageing rodents) is unlikely to be of relevance to humans. Vildagliptin-related hormonal influence on mammary tissue was confirmed by gene expression data from samples of mammary gland obtained from mice treated with vildagliptin for up to 53 weeks. These changes are unlikely to be of relevance to man, particularly at such high systemic exposure multiples.
Reproductive toxicity A complete reproductive toxicity package in rats and rabbits did not indicate reproductive toxic potential. In rats, vildagliptin is excreted in the milk at increased concentration compared with plasma.	Reproductive toxicity studies in animals suggest no adverse effects. However, there is no clinical experience in pregnant women.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

An aggregate analysis of 58 interventional Phase II and III clinical trials with treatment periods ranging from 12 to ≥ 104 weeks duration was performed to assess the safety of vildagliptin. The latest safety pool (all studies completed by December 2013) includes global studies as well as registration studies conducted primarily in Japan or China to support vildagliptin approval in these two countries. The 58 studies included in the analysis assessed vildagliptin as monotherapy, as add-on therapy to other antidiabetic agents (metformin, Thiazolidine (TZD), Sulfonylurea (SU) and insulin) and as initial combination therapy with metformin or pioglitazone, used at 50 mg qd, 50 mg bid or 100 mg qd dose. Patients not receiving vildagliptin (all comparators group) were taking placebo only (placebo group) or metformin, TZD, SU, acarbose or insulin (active comparators group). Some of the studies had long-term extensions. Exposure from the safety pool is presented for total vildagliptin and total comparators by duration, demographic characteristics, and within special population subsets in the following tables.

Table 4-1 Clinical trial exposure and treatment (all studies safety population excluding open label) by mutually exclusive categories of duration

Type 2 diabetes mellitus patients		
Duration of exposure	**Number of patients**	
	Vildagliptin (mono + add-on) N= 12008	**Total comparators (Placebo + Active comparators) N= 8068**
≥ 0 to < 12 weeks	1255 (10.5%)	925 (11.5%)
≥ 12 to < 24 weeks	1878 (15.6%)	1410 (17.5%)
≥ 24 to < 48 weeks	4072 (33.9%)	2507 (31.1%)
≥ 48 to < 52 week	604 (5.0%)	325 (4.0%)
≥ 52 weeks	4199(35.0%)	2901(36.0%)

Source: RMP version 14.1 Attachment to Annex 7 Table 1.2-2.1.

Table 4-2 Clinical trial exposure and treatment (all studies safety population including open label) by mutually exclusive categories of duration

Type 2 diabetes mellitus patients		
Duration of exposure	**Number of patients**	
	Vildagliptin (mono + add-on) N=14577	**Total comparators (Placebo + Active comparators) N= 8940**
≥ 0 to < 12 weeks	1778 (12.2%)	1173 (13.1%)
≥ 12 to < 24 weeks	3185 (21.8%)	2034 (22.8%)
≥ 24 to < 48 weeks	4160 (28.5%)	2507 (28.0%)
≥ 48 to < 52 week	970 (6.7%)	325 (3.6%)
≥ 52 weeks	4484 (30.8%)	2901 (32.4%)

Source: RMP version 14.1 Attachment to Annex 7 Table 1.2-1.1.

Table 4-3 Clinical trial exposure by dose (all studies safety population excluding open label)

Type 2 diabetes mellitus patients		
Vildagliptin	**Number of patients (N)**	**Patient-years**
All Vilda 50 mg once daily	2857	1761.7
All Vilda 50 mg twice a day	7474	7840.1
All Vilda 100 mg once daily	1677	778.1
Total Vilda	12008	10379.9
Comparators		
All Placebo	3071	1514.6
All active comparator	4997	5871.3
Total (Placebo + Active comparators)	8068	7385.9

Source: RMP version 14.1 Attachment to Annex 7 Table 1.2-2.1 and Table 1.2-2.2.

Table 4-4 Clinical trial exposure by dose (all studies safety population including open label)

Type 2 diabetes mellitus patients		
Vildagliptin	**Number of patients (N)**	**Patient-years**
All Vilda 50 mg once daily	3017	1896.2
All Vilda 50 mg twice a day	7911	8249.3
All Vilda 100 mg once daily	3649	1346.1
Total Vilda	14577	11491.6
Comparators		
All Placebo	3071	1514.6
All active comparator	5869	6063.9
Total (Placebo + Active comparators)	8940	7578.5

Source: RMP version 14.1 Attachment to Annex 7 Table 1.2-1.1 and Table 1.2-1.2.

Table 4-5 Clinical trial exposure by age, gender and treatment (all studies safety population excluding open label)

Type 2 diabetes mellitus patients		
	Number of patients	
	Vildagliptin (mono + add-on) N= 12008	**Total comparators (Placebo + Active comparators) N= 8068**
Mean age (years)	56.6	57.5
Age	**N (%)**	**N (%)**
< 65 years	9007 (75.0%)	5737 (71.1%)
≥ 65 years	3001 (25.0%)	2331 (28.9%)
< 75 years	11506 (95.8%)	7713 (95.6%)
≥ 75 years	502 (4.2%)	355 (4.4%)
Gender		
Male	6611 (55.1%)	4436 (55.0%)

Type 2 diabetes mellitus patients		
Female	5397 (44.9%)	3632 (45.0%)

Source: RMP version 14.1 Attachment to Annex 7 Table 1.1-2.1.

Table 4-6 Clinical trial exposure by race and treatment (all studies safety population excluding open label)

Race	Vildagliptin SYE	Total comparators (Placebo + Active), SYE
Caucasian	7561.2	5489.4
Black	360.0	162.8
Asian	1157.5	804.6
Hispanic/Latino	1156.0	798.6
Other	145.2	130.4

Source: RMP version 14.1 Attachment to Annex 7 Table 1.2-2.2e.

Table 4-7 Exposure for special populations (all studies safety population excluding open label)

Type 2 diabetes mellitus patients		
Populations	**Number of patients (Vildagliptin) N=12008**	**Number of patients (Total comparators) N=8068**
Renal impairment, eGFR (ml/min/1.73 m^2) by MDRD‡		
eGFR > 80 (normal)	7007 (58.4%)	4676 (58.0%)
eGFR ≥50 - ≤80 (mild)	4322 (36.0%)	2890 (35.8%)
eGFR ≥30 - <50 (moderate)	452 (3.8%)	333 (4.1%)
eGFR < 30 (severe)	221 (1.8%)	169 (2.1%)
Not recorded	6 (0%)	0 (0%)

eGFR- estimated Glomerular Filtration Rate; MDRD‡- Modification of Diet in Renal Disease equation
Source: RMP version 14.1 Attachment to Annex 7 Table 1.1-2.2.

Exposure in study CLAF237A23118 is presented separately as well as it was a dedicated safety study in patients with CHF, NYHA class I-III.

Table 4-8 Exposure for CHF population (study CLAF237A23118)

	CHF population	Number of patients		SYE (Vilda)
		Vilda N	Placebo N	
CLAF237A23118	NYHA classes I – II	81	78	71.8
CLAF237A23118	NYHA class III	47	48	44.1

Source: RMP version 14.1 Attachment to Annex 7 Table 14.3-1.2a

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Hypersensitivity to the active substance or to any of the excipients.	These patients are contraindicated.	No	Cases of hypersensitivity reactions have been reported in patients receiving Galvus/Eucreas, with the onset of the reaction occurring in the majority of cases within the first month of treatment.
Acute metabolic conditions such as ketoacidosis, lactic acidosis, or hyperosmolar state (including coma) within the past 6 months	These patients are contraindicated.	No	Patients with pre-existing metabolic acidosis/lactic acidosis treated with Eucreas are at increased risk for lactic acidosis/worsened lactic acidosis, which is an important identified risk for Eucreas based on the presence of metformin.
Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury or secondary forms of diabetes	Any other cause of diabetes beyond the targeted indication.	No	Galvus acts by increasing the level of insulin produced by the pancreas. It may not be effective in other forms of diabetes where pancreas is already damaged and do not have the potential to produce more insulin. Therefore, these forms of diabetes are not considered missing information.
A history within previous 6 months of cerebrovascular disease such as stroke, TIA	These diseases are more likely in diabetes population and would be potential confounders to the interpretation of safety (and potentially efficacy) data.	No	Adequate control of diabetes mellitus is well known to have positive outcome in cerebrovascular events, therefore these condition is not considered as missing information and the only reason it is excluded during clinical trial as they can act as potential confounders coming in the way

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			of actual study safety assessment.
Malignancy of an organ system (other than localized basal cell carcinoma of the skin) treated or untreated, within the past 5 years	There is a tendency of relapse in malignancies. These diseases would be potential confounders to the interpretation of safety (and potentially efficacy) data.	No	They are not true missing information as the drug is not known to alter the course of malignancy and the only reason they were excluded from CT as malignant diseases would be potential confounders to the interpretation of safety (and potentially efficacy) data.
Hepatic disorder defined as: acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension, history of imaging abnormalities that suggest liver disease (except hepatic steatosis)	These pre-existent diseases would be potential confounders to the interpretation of safety (and potentially efficacy) data.	No	Hepatic disorder are known to occur and are listed ADRs in the product label. DILI is an important identified risk in RMP. Therefore, hepatic disorder are not considered as missing information.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program

Type of special population	Exposure
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not included in the clinical development program
• Patients with renal impairment	Refer to Table 4-7 for renal impairment population.
• Patients with cardiovascular impairment	Refer to Table 4-8 for CHF population.
• Immunocompromised patients	Not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Refer to Table 4-6 for exposure in different ethnicities
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Source: RMP version 14.1 Attachment to Annex 7

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

Post-marketing (non-study) exposure for Galvus/Eucreas is provided in the below sections through 28-Feb-2019.

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in number of units of tablet containing active substance sold or worldwide sales volume in kilogram (kg) of active substance sold cumulatively (till 28-Feb-2019) during the review period and the defined daily dose (DDD). The cumulative sales volume of Galvus and Eucreas are 10,406,457 PTY and 17,643,849 PTY, respectively.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience

	EEA*	USA and Canada	Japan	ROW
Vildagliptin tablets 50 mg	1,477,541	0	3,687,222	5,227,098
Vildagliptin tablets 100 mg	0	0	0	14,595
Overall	**1,477,541**	**0**	**3,687,222**	**5,241,693**

EEA: European Economic Area; ROW: Rest of the World; USA: United States of America.

* Included sales from Switzerland.

The values in this table are calculated by using formulae in excel. The sum up values are rounded off and there might be a difference of ±1 to the totals.

This table includes cumulative data obtained from Feb 2007 to Feb 2019 from Novartis Pharma; from 2009 to Feb 2019 from Merck KGaA and from Oct 2006 to Feb 2019 from Sandoz International GmbH.

Source of data: PSUR (reporting period: 01-Mar-2018 to 28-Feb-2019).

Table 6-2 Estimated post-marketing (non-clinical trial) exposure per formulation

Formulation	Cumulative Until 28 Feb 2019	
	Amount sold (Tablets)	Estimated exposure (PTY)
Vildagliptin/metformin FDC tablets containing 50 mg vildagliptin	12,854,898,006	17,609,449
Vildagliptin/ Metformin FDC tablets containing 100 mg vildagliptin	14,246,400	34,400
Total	**12,869,144,406**	**17,643,849**

This table includes cumulative data obtained from International Birth Date (14-Nov-2007) through (28-Feb-2019).

Source of data: PSUR (reporting period: 01-Mar-2018 to 28-Feb-2019)

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

The potential for misuse or illegal purposes is considered negligible and inconsequential.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as this is not the initial RMP.

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as this is not the initial RMP.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as this is not the initial RMP.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

In view of current evidence spanning over 13 years without a causal association and no additional PV activities or RMP commitments ongoing for this risk (Pancreatic Cancer), Novartis proposed to remove this risk from the RMP in the initial submission of variation to update RMP under Procedure No. EMEA/H/C/WS1970. PRAC in its first assessment recommended to retain risk of pancreatic cancer as important potential risk in line with other GLP-1 based T2DM therapies. Pancreatic cancer was hence re-introduced as an important potential risk. During the review of RMP 15.1, submitted along with the response for first request for supplementary information (RSI), EMA recommended the removal of pancreatic cancer as an important potential risk. The assessment report stated “during the long experience of the use of vildagliptin, from the time of the MA (2007) until today, no data has emerged that indicates a substantially increased risk of pancreatic cancer with the use of vildagliptin that could influence the B/R for any of the respective products (Galvus/Eucreas). Therefore, and based on the definition of an important potential risk in the up-dated GVP module V, the risk for pancreas cancer with the use of vildagliptin could be removed from the RMP, since the risk is not considered crucial to the B/R balance for the products and no additional pharmacovigilance or risk minimisation measures are deemed necessary. However, as the potential risk for pancreas cancer with use of incretins is not fully evaluated, the risk should continuously be followed outside the RMP.” Thus, pancreatic cancer is removed as an important potential risk in this update.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Drug-induced liver injury

Table 8-1 Clinical trial data of Drug-induced liver injury

Risk	**Drug-induced liver injury**		
Frequency with 95% CI	**Number (%) of patients with hepatic adverse events (All studies [excl. open label] safety population)**		
		Total Vildagliptin N=12008	**Total Comparators N= 8068**
	AE, n (%)	172 (1.4)	135 (1.7)
	AE/100 SYE (95% CI)	1.67 (1.43, 1.94)	1.85 (1.55, 2.19)
	Source: RMP version 14.1 Annex 12 Tables: 2.3-2.1, 2.3-2.4		
	Incidence of treatment emergent persistent on-treatment liver enzymes elevations*		

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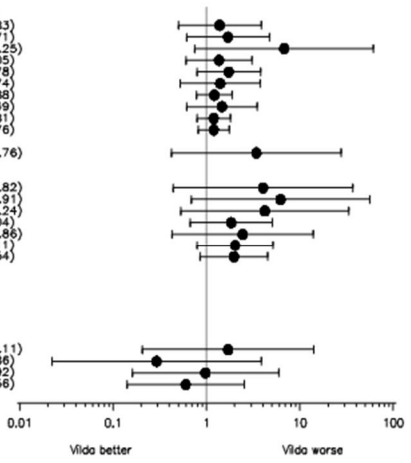
Figure 3.1–4.1 (Page 1 of 1)
Incidences and Incidence ratios for treatment emergent persistent on–treatment hepatic enzyme elevations by treatment
All studies (controlled, incl open–label) safety population

	Vilda n / N (%)	Reference n / N (%)	M–H RR (95% CI)
ALT/AST >= 3*ULN			
All: Vilda 50mg QD (vs. P)	9/ 1772 (0.51)	6/ 1918 (0.31)	1.38 (0.50– 3.83)
All: Vilda 50mg BID (vs. P)	10/ 1988 (0.50)	6/ 2088 (0.29)	1.70 (0.61– 4.71)
All: Vilda 100mg QD (vs. P)	8/ 624 (1.28)	1/ 537 (0.19)	6.78 (0.75– 61.25)
All: Vilda 50mg QD/BID (vs. P)	19/ 3760 (0.51)	10/ 2819 (0.35)	1.36 (0.61– 3.05)
All: Vilda (vs. P)	27/ 4384 (0.62)	10/ 2965 (0.34)	1.73 (0.79– 3.78)
All: Vilda 50mg QD (vs. C)	10/ 2197 (0.46)	7/ 2453 (0.29)	1.40 (0.52– 3.74)
All: Vilda 50mg BID (vs. C)	53/ 7207 (0.74)	35/ 6006 (0.58)	1.21 (0.78– 1.88)
All: Vilda 100mg QD (vs. C)	17/ 3185 (0.53)	8/ 2114 (0.38)	1.46 (0.61– 3.49)
All: Vilda 50mg QD/BID (vs. C)	63/ 9404 (0.67)	39/ 6950 (0.56)	1.19 (0.79– 1.81)
All: Vilda (vs. C)	80/12589 (0.64)	46/ 8522 (0.54)	1.20 (0.82– 1.76)
ALT/AST >= 5*ULN			
All: Vilda 50mg QD (vs. P)	4/ 1772 (0.23)	1/ 1918 (0.05)	3.42 (0.42– 27.76)
All: Vilda 50mg BID (vs. P)	2/ 1988 (0.10)	0/ 2088 (0.00)	
All: Vilda 100mg QD (vs. P)	4/ 624 (0.64)	0/ 537 (0.00)	
All: Vilda 50mg QD/BID (vs. P)	6/ 3760 (0.16)	1/ 2819 (0.04)	4.02 (0.44– 36.82)
All: Vilda (vs. P)	10/ 4384 (0.23)	1/ 2965 (0.03)	6.21 (0.69– 55.91)
All: Vilda 50mg QD (vs. C)	5/ 2197 (0.23)	1/ 2453 (0.04)	4.20 (0.53– 33.24)
All: Vilda 50mg BID (vs. C)	13/ 7207 (0.18)	6/ 6006 (0.10)	1.83 (0.67– 5.04)
All: Vilda 100mg QD (vs. C)	6/ 3185 (0.19)	2/ 2114 (0.09)	2.44 (0.43– 13.88)
All: Vilda 50mg QD/BID (vs. C)	18/ 9404 (0.19)	7/ 6950 (0.10)	2.02 (0.80– 5.11)
All: Vilda (vs. C)	24/12589 (0.19)	9/ 8522 (0.11)	1.96 (0.85– 4.54)
ALT/AST >= 3*ULN and Bilirubin > 1.5*ULN			
All: Vilda 50mg QD (vs. P)	0/ 1767 (0.00)	1/ 1916 (0.05)	
All: Vilda 50mg BID (vs. P)	0/ 1988 (0.00)	0/ 2088 (0.00)	
All: Vilda 100mg QD (vs. P)	0/ 624 (0.00)	0/ 537 (0.00)	
All: Vilda 50mg QD/BID (vs. P)	0/ 3755 (0.00)	1/ 2817 (0.04)	
All: Vilda (vs. P)	0/ 4379 (0.00)	1/ 2963 (0.03)	
All: Vilda 50mg QD (vs. C)	0/ 2191 (0.00)	1/ 2450 (0.04)	
All: Vilda 50mg BID (vs. C)	3/ 7196 (0.04)	1/ 5997 (0.02)	1.70 (0.21– 14.11)
All: Vilda 100mg QD (vs. C)	1/ 3019 (0.03)	2/ 2025 (0.10)	0.29 (0.02– 3.86)
All: Vilda 50mg QD/BID (vs. C)	3/ 9387 (0.03)	2/ 6939 (0.03)	0.97 (0.16– 5.92)
All: Vilda (vs. C)	4/12406 (0.03)	4/ 8422 (0.05)	0.60 (0.14– 2.56)



Arrows represent estimates outside of axis range.
n = Number of patients meeting the criterion (i.e. who are notably abnormal). N = Number of patients with evaluable criterion.
Notable abnormalities summarized are those which are treatment emergent (i.e. not present at any pre–treatment visit).
Persistent elevations are those which meet the criterion at consecutive on–treatment measurements or at last on–treatment visit.
Risk ratios estimates only include studies with at least one event.
/report/pgm_saf/f_hep_41.sas●●/main/1 21MAR14:12:55 Final Version

* Analysis from pooled safety population, including controlled open label studies Source: RMP version 14.1 Annex 12 Figure 3.1-4.1

Seriousness/Outcomes	**Number (%) of patients with hepatic serious adverse events (All studies [excluding open label] safety population)**	

Risk	Drug-induced liver injury

	Total Vildagliptin N=12008	Total Comparators N= 8068
SAE, n (%)	16 (0.1)	9 (0.1)
SAE/100SYE	0.15	0.12
Discontinuations n (%)	24 (0.2)	15 (0.2)

Source: RMP version 14.1 Annex 12 Tables: 2.3-2.2, 2.3-2a.2, 2.3-2.3

Frequency and severity analysis - Post-authorization experience from Novartis Safety database (ARGUS):

Frequency and severity analysis of transaminase increased and DILI cases – Galvus

Comparing frequency at different periods			Comparing severity at different periods
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	30	0.19	4
Last PSUR*	81	0.57	4
Cumulatively	2,105	2.02	116
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Frequency and severity analysis of the transaminase increased and DILI cases – Eucreas

Comparing frequency at different periods			Comparing severity at different periods
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	53	0.17	3
Last PSUR*	55	0.20	4
Cumulatively	752	0.43	39
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Post-authorization experience based on data from non-interventional PASS CLAF237A2401 is presented below.

Relative risk estimates (presented as adjusted incidence rate ratios [IRRs]) on ALT or AST > 3-times ULN and bilirubin >2-times ULN, ALT or AST > 10-times ULN (only performed in CPRD GOLD) as well as on serious hepatic events available from non-interventional PASS CLAF237A2401 study are presented in the below tables.

Adjusted incidence rate ratios of ALT or AST > 3-times ULN and bilirubin >2-times ULN or ALT or AST > 10-times ULN in CPRD GOLD for vildagliptin overall, vildagliptin single agent and vildagliptin/metformin fixed-dose combination (data from PASS CLAF237A2401)

Risk	Drug-induced liver injury

	CPRD GOLD (UK)			
	ALT or AST > 3-times ULN and bilirubin >2-times ULN		ALT or AST > 10-times ULN	
	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value
Vildagliptin overall	0.72 (0.42-1.25)	1.0	1.61 (0.51-5.08)	1.0
Vildagliptin single agent	0.76 (0.36-1.60)	1.0	3.20 (0.99-10.31)	1.0
Vildagliptin/metformin FDC	0.77 (0.36-1.63)	1.0	NA	NA

Adj. = adjusted; CI = confidence interval; FDC = fixed-dose combination; IRR = incidence rate ratio; NA = not applicable (zero events in the vildagliptin group); ULN = upper limit of normal; UK = United Kingdom Source: Williams et al 2015

Adjusted incidence rate ratios of serious hepatic events across five databases for vildagliptin overall, vildagliptin single agent and vildagliptin/metformin fixed-dose combination (data from CLAF237A2401)

	CPRD GOLD (UK)		IMS DA Germany		IMS DA France		OPED (Den)		National Registers (Swe)	
	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95 % CI)	Adj. p-value
Vildagliptin overall	0.43 (0.11-1.71)	1.0	0.55 (0.47-0.65)	.02	0.29 (0.13-0.63)	.03	0.36 (0.05-2.72)	1.0	NA	NA
Vildagliptin single agent	0.42 (0.06-3.00)	1.0	0.45 (0.33-0.60)	.02	0.44 (0.10-1.94)	1.0	NA	NA	NA	NA
Vildagliptin/metformin FDC	0.42 (0.06-2.99)	1.0	0.59 (0.49-0.71)	.02	0.25 (0.10-0.63)	.03	0.44 (0.06-3.36)	1.0	NA	NA

Adj. = adjusted; CI = confidence interval; DA = Disease Analyzer; Den = Denmark; FDC = fixed-dose combination; IRR = incidence rate ratio; OPED = Odense PharmacoEpidemiological Database; UK = United Kingdom

Source: Willams et al 2015

Conclusion: Cumulative analysis of the Novartis Safety database (ARGUS) did not reveal any new safety concern regarding the risk of DILI cases. The safety profile of Galvus and Eucreas related to DILI remains unchanged.

Table 8-2 Important identified risk Drug-induced liver injury: Other details

Name of the risk Drug-induced liver injury	Details
Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	**Incidence** In a population-based cohort study in the UK among 44,406 T2DM patients with oral antidiabetic treatment, 605 patients developed a first-time computer-recorded diagnosis of liver disease that occurred within 90 days after receiving a prescription for an oral antidiabetic drug. The IR of liver disease was 53.2 (95% CI 49.2-57.6) per 10,000 PY (Jick et al 1999). In a population-based matched retrospective cohort study using information from administrative health databases from the province of Ontario, Canada, Porepa et al (2010) found an incidence rate of 8.19 per 10,000 PYs for any serious liver disease (defined as liver cirrhosis, liver failure and its sequelae, or liver transplantation) in 438,069 adults (30-75 years of age) with newly diagnosed diabetes after excluding those with pre-existing liver or alcohol-related diseases. The corresponding incidence rate of liver failure (and sequelae) was 5.84 per 10,000 PYs. The risk of advanced hepatopathy was found to be higher in the group of patients with newly diagnosed diabetes as compared to an age-, sex- and region-matched comparison group without diabetes (adjusted hazard ratio: 1.77; 95% CI 1.68-1.86). **Prevalence** Salmela et al (1984) assessed the prevalence of abnormal liver function tests (LFTs) of nine different test parameters in a total of 175 diabetic out- and 72 diabetic in patients with type 1 and type 2 diabetes in Oulo, Finland. The prevalence of abnormal AST (i.e. > 40 IU/L), ALT (i.e. > 40 IU/L) and bilirubin (i.e. > 17 IU/L) in 118 T2DM outpatients was 5.1%, 22.9%, and 10.2%, respectively. West et al (2006) assessed the prevalence of elevated ALT in type 1 and 2 diabetic patients from Nottingham (UK). Elevated ALT was found in 12.1% (95% CI 9.9-14.5%) of those with T2DM. The risk of elevated ALT in T2DM patients increased with increasing BMI (p trend = 0.04), and was lower in those taking insulin (OR 0.38, 95% CI 0.22–0.65). The authors concluded that the prevalence of elevated ALT is 3- to 4-times higher in patients with either type 1 or type 2 diabetes than in the general population assuming a prevalence of elevated ALT of approximately 3% in the general population. In a population based cohort study in the UK, the incidence rate of liver disease was 53.2 per 10,000 patient years. In the UK, a prevalence of elevated ALT of approximately 12% was estimated for patients with either type 1 or type 2 DM corresponding to a 3- to 4-times higher prevalence than in the general population. The prevalence of AST>40 IU/L, ALT>40 IU/L, and bilirubin>17 IU/L among 118 outpatients with type 2 DM in Finland was 5.1%, 22.9%, and 10.2%, respectively. (Tolman et al 2007).
Characterization of the risk:	Rare case of hepatic dysfunction were seen during development program of vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and LFTs returned to normal after discontinuation of treatment. Similar findings of hepatic dysfunction were confirmed by literature. From the clinical trial data presented in Table 8-2, there is no imbalance in the hepatic Adverse Events (AEs) and Serious Adverse Events (SAEs)

Name of the risk Drug-induced liver injury	Details
	between the Total vildagliptin and the Total comparators groups. The hepatic enzyme analysis indicates that vildagliptin was associated with a slightly higher risk (statistically not significant) of persistent ≥ 3x ULN and ≥ 5x ULN transaminase elevations relative to all comparators. There is no evidence of an increased risk of persistent transaminase elevations with concomitant bilirubin elevation >1.5xULN with vildagliptin. Hence, the risk of liver function tests elevation considered to be more specific for potential drug-induced hepatotoxicity is low and similar between vildagliptin and all comparators.
Risk factors and risk groups	Patients with Hepatic impairment.
Preventability	Vildagliptin is not recommended in patients with hepatic impairment. LFT monitoring is recommended at initiation of therapy and at 3 month intervals in the first year and periodically thereafter.
Impact on the benefit-risk balance of the product	Based on available information, the impact on the benefit risk balance of product is expected to be low.
Public health impact	Minimal.

8.3.1.2 Important Identified Risk: Acute pancreatitis

Table 8-3 Clinical trial data of Acute pancreatitis

Risk	**Acute pancreatitis**		
Frequency with 95% CI		**Total Vildagliptin N=12008**	**Total Comparators N=8068**
	AE, n (%)	34 (0.3)	20 (0.2)
	AE/100 SYE (95% CI)	0.33 (0.23, 0.46)	0.27 (0.17, 0.42)
	Source: RMP version 14.1 Annex 12 Tables: 2.3-2.1, 2.3-2.5		
Seriousness /Outcomes		**Total Vildagliptin N=12008**	**Total Comparators N=8068**
	SAE n (%)	7 (0.1)	6 (0.1)
	SAE/ 100SYE	0.1	0.1
	Discontinuations n (%)	4 (0.03)	5(0.06)
	Source: RMP version 14.1 Annex 12 Tables: 2.3-2.2, 2.3-2a.2, 2.3-2.5, 2.3-2.3		
	Frequency and severity analysis - Post-authorization experience from Novartis Safety database (ARGUS):		
	Frequency and severity analysis of acute pancreatitis cases – Galvus		

Risk **Acute pancreatitis**

Comparing frequency at different periods			Comparing severity at different periods
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	25	0.16	3
Last PSUR*	31	0.22	1
Cumulatively	407	0.39	30
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Frequency and severity analysis of acute pancreatitis cases –Eucreas

Comparing frequency at different periods			Comparing severity at different periods
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	25	0.08	0
Last PSUR*	32	0.11	0
Cumulatively	452	0.26	0
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Post-authorization experience based on data from non-interventional PASS CLAF237A2401 is presented below.

Relative risk estimates (presented as adjusted incidence rate ratios [IRRs]) on acute pancreatitis available from non-interventional PASS CLAF237A2401 are presented in the following table.

Adjusted incidence rate ratios of acute pancreatitis across five databases for vildagliptin overall, vildagliptin single agent and vildagliptin/metformin fixed-dose combination (data from PASS CLAF237A2401)

	CPRD GOLD (UK)		**IMS DA Germany**		**IMS DA France**		**OPED (Den)**		**National Registers (Swe)**	
	Adj. IRR (95% CI)	**Adj. p-value**	**Adj. IRR (95% CI)**	**Adj. p-value**	**Adj. IRR (95 % CI)**	**Adj. p-value**	**Adj. IRR (95% CI)**	**Adj. p-value**	**Adj. IRR (95% CI)**	**Adj. p-value**
Vildagliptin overall	0.90 (0.22-3.60)	1.0	0.89 (0.65-1.24)	1.0	NA	NA	NA	NA	2.58 (0.65-10.35)	1.0
Vildagliptin single agent	1.77 (0.44-7.10)	1.0	0.98 (0.54-1.78)	1.0	NA	NA	NA	NA	1.78 (0.25-12.64)	1.0

Risk	**Acute pancreatitis**										
	Vildagliptin/metformin FDC	NA	NA	0.87 (0.60-1.27)	1.0	NA	NA	NA	NA	4.66 (0.66-33.10)	1.0

Source: Williams et al 2015

Conclusion: Cumulative analysis of the Novartis Safety database (ARGUS) did not reveal any new safety concern regarding the risk of acute pancreatitis. The safety profile of Galvus and Eucreas related to acute pancreatitis remains unchanged

Table 8-4 Important identified risk Acute pancreatitis: Other details

Name of the risk Acute pancreatitis.	**Details**
Potential mechanisms	The pathogenesis of pancreatitis involves release of pancreatic exocrine enzymes, typically precipitated by situations involving decreased biliary tract motility, which can be due to mechanical obstruction or functional abnormality, as seen in insulin resistance. There appears to be no physiological mechanism for therapeutic inhibition of DPP-IV with vildagliptin to cause acute pancreatitis. In pre-clinical toxicology studies with vildagliptin no pancreatic toxicities were observed. Post-marketing cases of acute pancreatitis have been reported with GLP-1 based therapies. The mechanism has not been identified, but hypothetically might be related to: - Overgrowth of pancreatic duct cells resulting in occasional obstruction of the smallest ducts, with the potential to cause subclinical pancreatic inflammation, and acute pancreatitis in rare instances -Delay in gastric emptying can lead to gastric distension, stimulating sphincter of Oddi motility, which could represent a potential indirect mechanism for GLP-1 agonists to cause pancreatitis. However, vildagliptin does not cause a delay in gastric emptying (Vella et al 2007).
Evidence source(s) and strength of evidence	**Incidence** Gonzalez-Perez et al (2010) performed a population based nested case-control analysis nested in a cohort of 85,525 type 2 diabetes (average age at study start 61.2 years; 43.7% females) and a random sample of 200,000 diabetes-free individuals from the general population aged 20-79 years using data from The Health Improvement Network (THIN), an electronic primary care medical record database from the UK. Patients with a history of cancer (excluding non-melanoma skin cancer) or pancreatic disease were excluded. Age- and sex-stratified AP incidence rates were calculated in the type 2 diabetic cohort based on 176 cases and a total of 325,990 PYs of follow-up: AP incidence rates (with 95% CIs) per 100,000 PY Age (yrs) / Males / Females / Overall 20 – 39: 44.7 (5.4-161.3) / 78.4 (21.3-200.6) / -- 40 – 59: 57.3 (39.8-79.6) / 51.7 (32.0-79.1) / -- 60 – 69: 50.0 (34.2-70.6) / 59.5 (39.2-86.5) / -- 70 – 79: 59.7 (41.0-83.8) / 43.9 (27.5-66.5) / -- Overall: 55.2 (44.9-66.9) / 52.4 (41.1-65.8) / 54.0 (46.3-62.5)

Name of the risk Acute pancreatitis.	Details
	In the cohort analysis of the same study, the age-, sex-, and calendar year-adjusted incidence rate ratio of AP in diabetic patients versus that in the general population was 1.77 (95% CI 1.46-2.15). The magnitude of this association decreased with adjustment for various additional factors in the nested case-control analysis (adjusted OR 1.37; 95% CI 0.99-1.89) (Gonzalez-Perez et al 2010). A slightly higher overall incidence rate was identified by Girman et al (2010) in a cohort study based on data from the General Practice Research Database (GPRD). The AP incidence rate identified in T2DM patients (including those with a previous history of pancreatitis) was 65.9 per 100,000 PYs. The risk of developing AP was approximately 50% higher in patients with T2DM as compared to patients without diabetes (adjusted hazard ratio 1.49; 95% CI: 1.31-1.70). In addition, various cohort studies from the United States (US) with secondary use of data from administrative health claims databases have been published reporting AP incidence rates ranging approximately from 130-560/100,000 person-years (e.g. Noel et al 2009, Garg et al 2010, Romley et al 2012, Wenten et al 2012); however, these health claims data may overestimate the AP incidence rates, e.g. due to claims miscoding for pancreatitis, or population differences (Noel et al 2009). Furthermore, studies have been published from Taiwan (Lai et al 2011, Shen et al 2012a) and Japan (Urushihara et al 2012) based on claims or hospital administrative data reporting AP incidence rates similar to the ones from the US in the range of 280-480/100,000 person-years. **Prevalence** In a cohort of 218,874 T2DM patients with at least one prescription for an oral antidiabetic drug (other than sitagliptin) identified from a US health claims database, the prevalence of a pancreatitis in the previous 12 months was 0.5% (Cai et al 2010). In chronic pancreatitis about 60% of the patients are reported to have diabetes, 30% to be insulin-dependent (Hardt et al 2002). **Mortality** Data on mortality of AP in T2DM patients are scarce. A retrospective cohort study using the Taiwanese National Health Insurance Research Database found that the hospital mortality in diabetic first-attack AP patients was 3.5% vs 4.1% in non-diabetic patients (adjusted OR 0.77; 95% CI 0.65-0.91) (Shen et al 2012b). Data from the general population suggest that the case fatality rate of AP decreased from 20% in the early 1960s to 6% in the year 2000 (Yadav and Lowenfels 2006). The case fatality was less than 5% for the age group < 40 years but increased to 28% in those older than 60 years and was 30-40% in those older than 80 years old. However, the reported case fatality rate of first attack of AP in studies published since 2000 ranges from 3% to 10.7% (Spanier et al 2008).
Characterization of the risk:	Literature reports; post-marketing reports of pancreatitis. From the clinical trial data presented in Table 8-4, overall, pancreatitis-related AEs and SAEs were reported infrequently with similar incidences across the Total vildagliptin and the Total comparators groups. Whilst reports of pancreatitis have been received from post marketing, the events have generally not been severe and for events where outcome is reported,

Name of the risk Acute pancreatitis.	Details
	the events have either resolved whilst still on drug or after drug withdrawal. These cases are on the background of higher rates of pancreatitis in patients with T2DM than patients without diabetes (Noel et al 2009, Girman et al 2010, Gonzalez-Perez et al 2010, Yang et al 2013).
Risk factors and risk groups	Diabetics have a higher incidence of pancreatitis and biliary disease than individuals without diabetes. A meta-analysis of non-interventional studies showed that T2DM is associated with an increased AP risk (relative risk =1.84; 95% CI 1.45-2.33) (Yang et al 2013). Typical risk factors for AP probably also apply for T2DM patients and include e.g. advanced age, race (higher among black than white population), alcohol, smoking, obesity, gallstones, hypertriglyceridemia (Yadav and Lowenfels 2013).
Preventability	Unknown.
Impact on the benefit-risk balance of the product	Caution should be exercised in patients with a history of acute pancreatitis. Considering that acute pancreatitis is observed uncommonly and is usually reversible on treatment, the impact on benefit risk profile is expected to be low.
Public health impact	Unknown.

8.3.1.3 Important Identified Risk: Lactic acidosis (Eucreas only)

Table 8-5 Clinical trial data of Lactic acidosis

Risk	Lactic acidosis
Frequency with 95% CI	Not applicable as no clinical trial cases were reported
Seriousness/ Outcomes	Serious – No serious cases were reported **Frequency and severity analysis - Post-authorization experience from Novartis Safety database (ARGUS):** **Frequency and severity analysis of lactic acidosis cases – Eucreas**

Comparing frequency at different periods			Comparing severity at different periods
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	36	0.11	21
Last PSUR*	24	0.09	9
Cumulatively	157	0.09	83
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Post-authorization experience based on data from non-interventional PASS CLAF237A2401 is presented below.

Relative risk estimates (presented as adjusted incidence rate ratios [IRRs]) on lactic acidosis available from non-interventional PASS CLAF237A2401 for vildagliptin/metformin FDC are presented in the following table.

Adjusted incidence rate ratios of lactic acidosis across five databases for vildagliptin/metformin fixed-dose combination (data from CLAF237A2401)

Risk	Lactic acidosis									
	CPRD GOLD (UK)		IMS DA Germany		IMS DA France		OPED (Den)		National Registers (Swe)	
	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95% CI)	Adj. p-value	Adj. IRR (95 % CI)	Adj. p-value
Vildagliptin/metformin FDC	NA	NA	0.29 (0.04-2.35)	1.0	42.66 (0.27-6796.79)	1.0	2.97 (0.72 - 12.26)	1.0	NA	NA

Source: Williams et al 2015

Conclusion: Cumulative analysis of the Novartis Safety database (ARGUS) did not reveal any new safety concern regarding the risk of lactic acidosis. The safety profile of Eucreas related to lactic acidosis remains unchanged.

Table 8-6 Important identified risk Lactic acidosis: Other details

Name of the risk Lactic acidosis.	Details
Potential mechanisms	Metformin, along with other drugs in the biguanide class, increases plasma lactate levels in a plasma concentration-dependent manner by inhibiting mitochondrial respiration predominantly in the liver.
Evidence source(s) and strength of evidence	**Incidence** The incidence rate of lactic acidosis in T2DM patients in the US (before metformin was introduced) was reported to be 9.7 (95% CI: 0.2 to 19.1) cases per 100,000 PYs (Brown et al 1998). Salpeter et al (2006) performed a systemic literature review to assess the incidence of fatal and nonfatal lactic acidosis with metformin use compared to placebo and other glucose-lowering treatments in patients with T2DM. Pooled data from 206 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 47,846 PYs of metformin use or in 38,221 PYs in the non-metformin group. The upper limit of the 95% CI of the estimated incidence rate of metformin-associated lactic acidosis was 6.3 cases per 100,000 PYs, the corresponding figure in the non-metformin group was 7.8 cases per 100,000 PYs. Bodmer and colleagues performed a nested case-control analysis using the U.K.-based General Practice Research Database to identify T2DM patients who used oral antidiabetic drugs. Within the study population, all incident cases of lactic acidosis were identified. Among the study population of 50,048 T2DM subjects, six cases of lactic acidosis during current use of oral antidiabetic drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 PYs among metformin users and 4.8 cases per 100,000 PYs among users of sulfonylureas (Bodmer et al 2008). **Prevalence** No information on period or point prevalence of lactic acidosis in T2DM patients unexposed to metformin could be identified. **Mortality**

Name of the risk Lactic acidosis.	**Details**
	No information on the mortality rate of lactic acidosis in T2DM patients unexposed to metformin could be identified. In critically ill patients admitted to the intensive care unit of a US tertiary hospital, the case fatality was 56% for patients with lactic acidosis (n=239) (Gunnerson et al 2006). In a French case-series of 49 metformin-treated patients with lactic acidosis, the case fatality rate was 45% (Lalau and Race 1999).
Characterization of the risk:	Review of cumulative data from consolidated Galvus/Eucreas PSUR (01-Mar-2018 to 28-Feb-2019) did not identify any new signals regarding lactic acidosis.
Risk factors and risk groups	Age may be a risk factor due to declining renal function. High overdose of metformin. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Severe renal impairment (GFR <30 mL/min) Acute conditions with the potential to alter renal function, such as: • dehydration, • severe infection, • shock, • intravascular administration of iodinated contrast agents Surgery Alcohol intoxication
Preventability	Contraindication of use in presence of any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) Contraindication of use in patients with e-GFR < 30 mL/min. Renal function screen in susceptible patients. GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. Dose reduction of metformin may be considered in relation to declining renal function. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently e.g., every 3 - 6 months. Interruption of metformin therapy in patients at risk of lactic acidosis. Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
Impact on the benefit-risk balance of the product	Considering that lactic acidosis is observed very rarely with metformin. Though the event is usually serious but it often resolves on supportive treatment. Overall, the impact on benefit risk profile of drug is expected to be low.
Public health impact	Minimal.

8.3.1.4 Important Potential Risk: Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)

Table 8-7 Clinical trial data of Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)

Risk	**Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use** (events of myalgia excluded)	
Frequency with 95% CI	**Muscle events (NMQ search) with and without concurrent statin use**	
	Total Vildagliptin N=12008	**Total Comparators N=8068**
AE, n (%)	244 (2.0)	175 (2.2)
AE/100 SYE (95% CI)	2.38 (2.09, 2.70)	2.41 (2.07, 2.80)
Muscle events with concurrent statin use		
	Total vildagliptin N=3698	**Total comparators N=2713**
AE, n (%)	130 (3.5)	80 (3.0)
AE/100 SYE	3.57	2.95
Muscle events without concurrent statin use		
	Total vildagliptin N=8310	**Total comparators N=5355**
AE, n (%)	114 (1.4)	95 (1.8)
AE/100 SYE	1.69	2.03
Source: RMP version 14.1 Annex 12 Tables 2.3-2.1, 2.3-2.8, 2.3-2.1g, 2.3-2a.1g, 2.3-2a.1g.2		
Number (%) of patients with rhabdomyolysis/myopathy (SMQ broad search; All studies [excluding open label] safety population)		
With and without concurrent statin use		
	Total Vildagliptin N=12008	**Total Comparators N= 8068**
AE, n (%)	556 (4.6)	421 (5.2)
AE/100SYE (95% CI)	5.56 (5.10, 6.04)	5.97 (5.41, 6.57)
With concurrent statin use		
	Total Vildagliptin N=3698	**Total Comparators N= 2713**
AE, n (%)	286 (7.7)	206 (7.6)
AE/100SYE	7.9	7.6
Without concurrent statin use		
	Total Vildagliptin N=8310	**Total Comparators N= 5355**
AE, n (%)	270 (3.2)	215 (4.0)
AE/100SYE	4.0	4.6
Source: RMP version 14.1 Annex. 7 Tables: 2.8-2.1, 2.8-2.3, 2.3-2.10, 2.8-2a.3.1, 2.8-2a.3.2		
Number (%) of patients with CPK elevations ≥ 10xULN (All studies [including open label] safety population)		

Risk	**Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use** (events of myalgia excluded)
Seriousness /Outcomes	**With and without concurrent statin use**

	Total Vildagliptin N=14577	**Total Comparators N= 8940**
AE, n (%)	4/12230 (0.0)	2/7578 (0.0)
AE/100SYE	0.03	0.03

With concurrent statin use

	Total Vildagliptin N=4717	**Total Comparators N= 3164**
AE, n (%)	2/3714 (0.1)	0/2562 (0.0)

Without concurrent statin use

	Total Vildagliptin N=9860	**Total Comparators N=5776**
AE, n (%)	2/8516 (0.0)	2/5016 (0.0)

Source: RMP version 14.1 Annex 12 Tables: 3.1-1.1, 3.1-1.1g, 3.1-1a.1

Muscle SAEs/discontinuations with and without concurrent statin use

	Total Vildagliptin N=12008	**Total Comparators N=8068**
SAE n (%)	4 (0.0)	1 (0.0)
SAE/ 100SYE	0.04	0.01
Discontinuations n(%)	19 (0.2)	6 (0.1)

Source: RMP version 14.1 Annex 12 Tables 2.3-2.2, 2.3-2a.2, 2.3-2.3

Number (%) of patients with rhabdomyolysis/myopathy SAEs (SMQ broad search; All studies [excluding open label] safety population)

Risk **Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use** (events of myalgia excluded)

With and without concurrent statin use

	Total Vildagliptin N=12008	**Total Comparators N= 8068**
SAE, n (%)	33 (0.3)	23 (0.3)
Discontinuations n (%)	46 (0.4)	20 (0.2)

With concurrent statin use

	Total Vildagliptin N=3698	**Total Comparators N=2713**
SAE, n (%)	21 (0.6)	17 (0.6)
SAE/100SYE	0.6	0.6

Without concurrent statin use

	Total Vildagliptin N=8310	**Total Comparators N=5355**
SAE, n (%)	12 (0.1)	6 (0.1)
SAE/100SYE	0.2	0.1

Source: RMP version 14.1 Annex 12 Tables: 2.8-2.1, 2.8-2.2, 2.8-2.3, 2.8-2a.3.1, 2.8-2a.3.2, 2.8-2.4, 2.8-2a.4.1, 2.8-2a.4.2, 2.8-2.5

Frequency and severity analysis - Post-authorization experience from Novartis Safety database (ARGUS):

Frequency and severity analysis of muscle events/myopathy with and without concurrent statin use – Galvus

Comparing frequency at different periods			**Comparing severity at different periods**
Period	**No of post marketing cases**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	12	0.08	0
Last PSUR*	16	0.11	0
Cumulatively	488	0.47	0
# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)			

Frequency and severity analysis of muscle events/myopathy with and without concurrent statin use – Eucreas

Comparing frequency at different periods			**Comparing severity at different periods**
Period	**No of post marketing cases (excluding PMS-POP cases)**	**Reporting Frequency (per 1,000 PTY)**	**No of fatal cases**
Current PSUR#	16	0.05	0
Last PSUR*	26	0.09	0
Cumulatively	224	0.13	0

Risk	**Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use** (events of myalgia excluded)
	# Reporting interval – (01-Mar-2018 to 28-Feb-2019), * Reporting interval – (01-Mar-2017 to 28-Feb-2018)
	Conclusion: Cumulative analysis of the Novartis Safety database (ARGUS) did not reveal any new safety concern regarding the risk of muscle events/myopathy with and without concurrent statin use. The safety profile of Galvus and Eucreas related to muscle events/ myopathy/ rhabdomyolysis, in particular with current statin use remains unchanged.

Table 8-8 Important potential risk Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded): Other details

Name of the risk Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use.	**Details**
Potential mechanisms	Diabetic patients are at increased risk of myopathy because diabetic neuropathy, impaired renal function, non-alcoholic fatty liver and other conditions and multiple concomitant medications all of which can increase their susceptibility to the statin-induced myopathy.
Evidence source(s) and strength of evidence	**Incidence** A comprehensive literature search revealed two cohort studies with information on the incidence of muscle events in T2DM patients. Both studies were based on information derived from large United States databases; one using electronic medical record information from a large Health Maintenance Organization (Kaiser Permanente Northwest [KPNW]), the other one using health claims information from a large managed care database (Integrated Healthcare Information Services [IHCIS]). The KPNW analysis assessed myopathic events (myalgia, myositis, myopathy, rhabdomyolysis) occurring during follow-up independent of any history of prior muscular events, while the IHCIS excluded those patients with a prior history and only included 'incident' cases. The incidence rates of myopathic events reported in the two studies were very similar, namely 24.2 and 18.9 per 1,000 person-years of follow-up for T2DM patients with and those without statin exposure, respectively in the KPNW analysis (Nichols and Koro 2007), and 16.5 per 1,000 person-years in the IHCIS analysis (in T2DM patients with or without statin exposure) (Koro et al 2008). It is unclear however to which extent less severe forms of myopathy, for instance mild myalgia or myositis, may have been under-represented in these databases thereby giving too low estimates of the incidence rates. Rhabdomyolysis is a very rare disease in the general population. In a retrospective population-based analysis using the UK-based General Practice Research Database, 25 patients out of 2.5 million in a base population of patients aged 20-75 years were found to have rhabdomyolysis between 1990 and 1999 (Black and Jick 2002). Most information on the incidence of rhabdomyolysis has come from observational studies in users of statins, a drug class often co-prescribed in T2DM patients.

Name of the risk Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use.	Details
	In a recent systematic review of cohort studies, the incidence of rhabdomyolysis in users of statins was reported to be 0.34 (95% CI 1.6-6.5) per 10,000 person-years among all statin users (except cerivastatin) (Law and Rudnicka 2006). Similar results were found by Graham et al (2004) who estimated the risk of rhabdomyolysis in patients treated with lipid-lowering drugs (including statins) in the ambulatory setting. The incidence rate for rhabdomyolysis with statin monotherapy was about 0.44 per 10,000 person-years of therapy. This rate increased to about 6 per 10,000 person-years for combination therapy with a fibrate. In the cohort study mentioned above by Nichols and Koro (2007) based on Kaiser Permanente Northwest data, the proportion of diabetic patients identified with rhabdomyolysis during follow-up was 0.12% (95% CI 0.05-0.18%) in those without and 0.13% (0.06-0.20%) in those with statin exposure. The corresponding adjusted incidence rates were 2 (95% CI 1-5) and 1 (95% CI 1-3) per 10,000 person-years, respectively in those without and with statin exposure. The incidence of the most common statin-associated muscle-related complaint, i.e. non-specific muscle pain or joint pain in the absence of elevated CK, is approximately 5% (Christopher-Stine 2006). **Prevalence** The etiology of muscle-related events (e.g. myopathy, muscle infarction or pyomyositis) in the diabetic population includes conditions such as neuropathy, peripheral vascular disease, infections and certain concomitant medications, particularly statins. Neuropathy is a highly prevalent complication of diabetes which may be associated for instance with lower extremity proximal myopathy. Hong et al (1998) assessed the significance of symptoms - suggestive of neuropathy in T2DM patients and non-diabetic controls matched for age and gender. More T2DM patients than controls experienced symptoms suggestive of lower extremity proximal myopathy (i.e. weakness climbing stairs: 42 vs. 19%, getting up from squatting position: 31 vs. 11%). Additionally, more T2DM patients than controls had weaker hip muscles (24 vs. 6%). Diabetic muscle infarction is a rare, painful and potentially serious complication in patients with poorly controlled DM. It is frequently misdiagnosed clinically as abscess, neoplasm, or myositis. It can be triggered by an ischemic event and causes extensive muscle necrosis through hypoxia-reperfusion injury and compartment syndrome. CK levels may be normal or slightly increased. Only a few cases with diabetic muscle infarction have been published. Due to difficulties in making the correct diagnosis and excluding other etiologies, it can be speculated that diabetic muscle infarction is under-diagnosed (Sahin et al 2005). Another rare muscle-related event that may occur in diabetics is pyomyositis. It is a pyogenic infection of the skeletal muscle that can lead to abscess formation. It commonly occurs in the tropics, but is

Name of the risk Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use.	Details
	also recognized in temperate climates, with Human immunodeficiency virus (HIV) infection and diabetes being the main predisposing factors (Crum 2004, Seah et al 2004). Since 1981 more than 330 cases have been published. The most common underlying medical condition in HIV-negative patients was diabetes which was observed in 19% of cases (Crum 2004). Molsted et al (2012) estimated the prevalence of musculoskeletal pain in Danish 951 patients with T2DM aged 18+ years using a self-administered validated questionnaire to assess the history of pain in three parts in the musculoskeletal system during the past 14 days, i.e. pain in the shoulder and neck, low-back pain, and pain in the arm, hand, knee and/or hip. Patients with T2DM had a significantly higher prevalence of musculoskeletal pain in all three areas in the body (52% for shoulder and neck pain, 60% for low-back pain, 71% for pain in arm, hand, knee and/or hip) compared to an age- and gender-matched sample of the general population from the same geographical region The prevalence of musculoskeletal pain was 1.7- to 2.1-times (p< 0.001) higher in T2DM patients than the control patients. **Mortality** No information on mortality due to rhabdomyolysis or other muscle-related events in T2DM patients could be identified.
Characterization of the risk:	Clinical trials: In a phase I dose ranging study (CLAF237102-A1) in healthy volunteers, myalgia was observed at 400 mg dosage and CPK elevation with myoglobinemia was observed at 600 mg in dose-ranging study in healthy volunteers. This finding were not clinically relevant at the lower, therapeutic doses (isolated CPK elevations at low rates similar to placebo). In a repeat phase I dose ranging study (CLAF237A2221), no clinically significant increases in CPK were observed and there was no myoglobinemia. Only one case of mild myalgia (no enzyme elevations) was observed in the 300 mg bid dosage. Monkey toxicology studies: acute toxicity symptoms in the monkey included edema in distal extremities associated with skeletal muscle necrosis and elevations of CPK.
Risk factors and risk groups	Patients treated concomitantly with statins are at increased risk of myopathy. Statins can cause different degrees of myopathy, ultimately leading to rhabdomyolysis and acute renal failure.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	The impact on benefit risk profile is expected to be low.
Public health impact	Minimal.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

None.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Drug-induced liver injury
	Acute pancreatitis
	Lactic acidosis*
Important potential risks	Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)
Missing information	None

*Applicable to Eucreas only

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- Drug-induced Liver Injury
- Acute pancreatitis
- Lactic acidosis (applicable to Eucreas only)
- Muscle events/myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)

These checklists are provided in Annex 4 of the RMP.

10.2 Part III.2. Additional pharmacovigilance activities

There are currently no planned or ongoing activities to assess the effectiveness of risk minimization measures

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None				
Category 3 - Required additional pharmacovigilance activities.				
None				

11 Part IV: Plans for post-authorization efficacy studies

Not applicable, as there are no post-authorization efficacy studies.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Drug-induced liver injury	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Acute pancreatitis	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Lactic acidosis*	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 SmPC Section 4.9 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
Important Identified Risks	
	Prescription only medicine.
Important Potential Risks	
Muscle events/myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)	**Routine risk communication:** SmPC Section 4.8 SmPC Section 4.9 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Prescription only medicine **Other routine risk minimization measures beyond the Product Information:** None.
Missing Information	
None	

* Applicable to Eucreas only

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in 12.1 Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
Drug-induced liver injury	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section2 PL Section 4 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse reaction. **Additional pharmacovigilance activities:** None.
Acute pancreatitis	**Routine risk minimization measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse reaction.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None.	**Additional pharmacovigilance activities:** None.
Lactic acidosis*	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 SmPC Section 4.9 PL Section 2 PL Section 4 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse reaction. **Additional pharmacovigilance activities:** None.
Important Potential Risks		
Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.9 PL Section 4 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse event. **Additional pharmacovigilance activities:** None.
Missing Information		
None		

* Applicable to Eucreas only

13 Part VI: Summary of the risk management plan for Galvus/Eureas (Vildagliptin/Vildagliptin-Metformin)

This is a summary of the risk management plan (RMP) for Galvus/Eucreas. The RMP details important risks of Galvus/Eucreas, how these risks can be minimized.

The Galvus/Eucreas summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Galvus/Eucreas should be used.

This summary of the RMP for Galvus/Eucreas should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Galvus/Eucreas's RMP. The three yearly periodic update of RMP as stated in Annex II (D) of SmPC is removed. The RMP would be updated as and when applicable.

13.1 Part VI: I. The medicine and what it is used for

Vildagliptin is also authorized for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

They contain vildagliptin and vildagliptin+metformin hydrochloride as active substances, respectively and they are given as oral tablets. The recommended daily dose of Galvus is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. The recommended daily dose of Eucreas is 100 mg vildagliptin, initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.

Further information about the evaluation of vildagliptin's benefits can be found in vildagliptin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/galvus

Further information about the evaluation of vildagliptin+metformin benefits can be found in vildagliptin+metformin EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/eucreas

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Galvus/Eucreas, together with measures to minimize such risks and the proposed studies for learning more about Galvus/Eucreas's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Galvus/Eucreas is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Galvus/Eucreas are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Galvus/Eucreas. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

Important identified risks	Drug-induced liver injury Acute pancreatitis Lactic acidosis*
Important potential risks	Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)
Missing information	None

*Applicable to Eucreas only

13.2.2 Part VI - II B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 13-2 Important identified risk Drug-induced liver injury

Evidence for linking the risk to the medicine	**Incidence** In a population-based cohort study in the UK among 44,406 T2DM patients with oral antidiabetic treatment, 605 patients developed a first-time computer-recorded diagnosis of liver disease that occurred within 90 days after receiving a prescription for an oral antidiabetic drug. The IR of liver disease was 53.2 (95% CI 49.2-57.6) per 10,000 PY (Jick et al 1999). In a population-based matched retrospective cohort study using information from administrative health databases from the province of

	Ontario, Canada, Porepa et al (2010) found an incidence rate of 8.19 per 10,000 PYs for any serious liver disease (defined as liver cirrhosis, liver failure and its sequelae, or liver transplantation) in 438,069 adults (30-75 years of age) with newly diagnosed diabetes after excluding those with pre-existing liver or alcohol-related diseases. The corresponding incidence rate of liver failure (and sequelae) was 5.84 per 10,000 PYs. The risk of advanced hepatopathy was found to be higher in the group of patients with newly diagnosed diabetes as compared to an age-, sex- and region-matched comparison group without diabetes (adjusted hazard ratio: 1.77; 95% CI 1.68-1.86). **Prevalence** Salmela et al (1984) assessed the prevalence of abnormal liver function tests (LFTs) of nine different test parameters in a total of 175 diabetic out- and 72 diabetic in-patients with type 1 and type 2 diabetes in Oulo, Finland. The prevalence of abnormal AST (i.e. > 40 IU/L), ALT (i.e. > 40 IU/L) and bilirubin (i.e. > 17 IU/L) in 118 T2DM outpatients was 5.1%, 22.9%, and 10.2%, respectively. West et al (2006) assessed the prevalence of elevated ALT in type 1 and 2 diabetic patients from Nottingham (UK). Elevated ALT was found in 12.1% (95% CI 9.9-14.5%) of those with T2DM. The risk of elevated ALT in T2DM patients increased with increasing BMI (p trend = 0.04), and was lower in those taking insulin (OR 0.38, 95% CI 0.22–0.65). The authors concluded that the prevalence of elevated ALT is 3- to 4-times higher in patients with either type 1 or type 2 diabetes than in the general population assuming a prevalence of elevated ALT of approximately 3% in the general population. In a population based cohort study in the UK, the incidence rate of liver disease was 53.2 per 10,000 patient years. In the UK, a prevalence of elevated ALT of approximately 12% was estimated for patients with either type 1 or type 2 DM corresponding to a 3- to 4-times higher prevalence than in the general population. The prevalence of AST>40 IU/L, ALT>40 IU/L, and bilirubin>17 IU/L among 118 outpatients with type 2 DM in Finland was 5.1%, 22.9%, and 10.2%, respectively. (Tolman et al 2007).
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Additional risk minimization measures:** None

Table 13-3 Important identified risk Acute pancreatitis risk

Evidence for linking the risk to the medicine	**Incidence** Gonzalez-Perez et al (2010) performed a population based nested case-control analysis nested in a cohort of 85,525 type 2 diabetics (average age at study start 61.2 years; 43.7% females) and a random sample of 200,000 diabetes-free individuals from the general population aged 20-79 years using data from The Health Improvement Network (THIN), an

electronic primary care medical record database from the UK. Patients with a history of cancer (excluding non-melanoma skin cancer) or pancreatic disease were excluded. Age- and sex-stratified AP incidence rates were calculated in the type 2 diabetic cohort based on 176 cases and a total of 325,990 PYs of follow-up:

AP incidence rates (with 95% CIs) per 100,000 PY

Age (yrs)	Males	Females	Overall
20 – 39	44.7 (5.4-161.3)	78.4 (21.3-200.6)	--
40 – 59	57.3 (39.8-79.6)	51.7 (32.0-79.1)	--
60 – 69	50.0 (34.2-70.6)	59.5 (39.2-86.5)	--
70 – 79	59.7 (41.0-83.8)	43.9 (27.5-66.5)	--
Overall	55.2 (44.9-66.9)	52.4 (41.1-65.8)	54.0 (46.3-62.5)

In the cohort analysis of the same study, the age-, sex-, and calendar year-adjusted incidence rate ratio of AP in diabetic patients versus that in the general population was 1.77 (95% CI 1.46-2.15). The magnitude of this association decreased with adjustment for various additional factors in the nested case-control analysis (adjusted OR 1.37; 95% CI 0.99-1.89) (Gonzalez-Perez et al 2010).

A slightly higher overall incidence rate was identified by Girman et al (2010) in a cohort study based on data from the General Practice Research Database (GPRD). The AP incidence rate identified in T2DM patients (including those with a previous history of pancreatitis) was 65.9 per 100,000 PYs. The risk of developing AP was approximately 50% higher in patients with T2DM as compared to patients without diabetes (adjusted hazard ratio 1.49; 95% CI: 1.31-1.70).

In addition, various cohort studies from the United States (US) with secondary use of data from administrative health claims databases have been published reporting AP incidence rates ranging approximately from 130-560/100,000 person-years (e.g. Noel et al 2009, Garg et al 2010, Romley et al 2012, Wenten et al 2012); however, these health claims data may overestimate the AP incidence rates, e.g. due to claims miscoding for pancreatitis, or population differences (Noel et al 2009). Furthermore, studies have been published from Taiwan (Lai et al 2011, Shen et al 2012a) and Japan (Urushihara et al 2012) based on claims or hospital administrative data reporting AP incidence rates similar to the ones from the US in the range of 280-480/100,000 person-years.

Prevalence

In a cohort of 218,874 T2DM patients with at least one prescription for an oral antidiabetic drug (other than sitagliptin) identified from a US health claims database, the prevalence of a pancreatitis in the previous 12 months was 0.5% (Cai et al 2010).

In chronic pancreatitis about 60% of the patients are reported to have diabetes, 30% to be insulin-dependent (Hardt et al 2002).

Mortality

Data on mortality of AP in T2DM patients are scarce. A retrospective cohort study using the Taiwanese National Health Insurance Research Database found that the hospital mortality in diabetic first-attack AP patients was 3.5% vs 4.1% in non-diabetic patients (adjusted OR 0.77; 95% CI 0.65-0.91) (Shen et al 2012b).

	Data from the general population suggest that the case fatality rate of AP decreased from 20% in the early 1960s to 6% in the year 2000 (Yadav and Lowenfels 2006). The case fatality was less than 5% for the age group < 40 years but increased to 28% in those older than 60 years and was 30-40% in those older than 80 years old. However, the reported case fatality rate of first attack of AP in studies published since 2000 ranges from 3% to 10.7% (Spanier et al 2008).
Risk factors and risk groups	Diabetics have a higher incidence of pancreatitis and biliary disease than individuals without diabetes. A recent meta-analysis of non-interventional studies showed that T2DM is associated with an increased AP risk (relative risk =1.84; 95% CI 1.45-2.33) (Yang et al 2013). Typical risk factors for AP probably also apply for T2DM patients and include e.g. advanced age, race (higher among black than white population), alcohol, smoking, obesity, gallstones, hypertriglyceridemia (Yadav and Lowenfels 2013).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 SmPC Section 4.8 PI Section 4 **Additional risk minimization measures**: None.

Table 13-4 Important identified risk Lactic acidosis (Eucreas only)

Evidence for linking the risk to the medicine	**Incidence** The incidence rate of lactic acidosis in T2DM patients in the US (before metformin was introduced) was reported to be 9.7 (95% CI: 0.2 to 19.1) cases per 100,000 PYs (Brown et al 1998). Salpeter et al (2006) performed a systemic literature review to assess the incidence of fatal and nonfatal lactic acidosis with metformin use compared to placebo and other glucose-lowering treatments in patients with T2DM. Pooled data from 206 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 47,846 PYs of metformin use or in 38,221 PYs in the non-metformin group. The upper limit of the 95% CI of the estimated incidence rate of metformin-associated lactic acidosis was 6.3 cases per 100,000 PYs, the corresponding figure in the non-metformin group was 7.8 cases per 100,000 PYs. Bodmer and colleagues performed a nested case-control analysis using the U.K.-based General Practice Research Database to identify T2DM patients who used oral antidiabetic drugs. Within the study population, all incident cases of lactic acidosis were identified. Among the study population of 50,048 T2DM subjects, six cases of lactic acidosis during current use of oral antidiabetic drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 PYs among metformin users and 4.8 cases per 100,000 PYs among users of sulfonylureas (Bodmer et al 2008). **Prevalence** No information on period or point prevalence of lactic acidosis in T2DM patients unexposed to metformin could be identified. **Mortality** No information on the mortality rate of lactic acidosis in T2DM patients unexposed to metformin could be identified.

	In critically ill patients admitted to the intensive care unit of a US tertiary hospital, the case fatality was 56% for patients with lactic acidosis (n=239) (Gunnerson et al 2006). In a French case-series of 49 metformin-treated patients with lactic acidosis, the case fatality rate was 45% (Lalau and Race 1999).
Risk factors and risk groups	Age may be a risk factor due to declining renal function. High overdose of metformin. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Severe renal impairment (GFR <30 mL/min) Acute conditions with the potential to alter renal function, such as: • dehydration, • severe infection, • shock, • intravascular administration of iodinated contrast agents Surgery Alcohol Intoxication
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 SmPC Section 4.9 PL Section 2 PL Section 4 **Additional risk minimization measures:** None.

Table 13-5 Important potential risk Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)

Evidence for linking the risk to the medicine	**Incidence** A comprehensive literature search revealed two cohort studies with information on the incidence of muscle events in T2DM patients. Both studies were based on information derived from large United States databases; one using electronic medical record information from a large Health Maintenance Organization (Kaiser Permanente Northwest [KPNW]), the other one using health claims information from a large managed care database (Integrated Healthcare Information Services [IHCIS]). The KPNW analysis assessed myopathic events (myalgia, myositis, myopathy, rhabdomyolysis) occurring during follow-up independent of any history of prior muscular events, while the IHCIS excluded those patients with a prior history and only included 'incident' cases. The incidence rates of myopathic events reported in the two studies were very similar, namely 24.2 and 18.9 per 1,000 person-years of follow-up for T2DM patients with and those without statin exposure, respectively in the KPNW analysis (Nichols and Koro 2007), and 16.5 per

1,000 person-years in the IHCIS analysis (in T2DM patients with or without statin exposure) (Koro et al 2008). It is unclear however to which extent less severe forms of myopathy, for instance mild myalgia or myositis, may have been under-represented in these databases thereby giving too low estimates of the incidence rates.

Rhabdomyolysis is a very rare disease in the general population. In a retrospective population-based analysis using the UK-based General Practice Research Database, 25 patients out of 2.5 million in a base population of patients aged 20-75 years were found to have rhabdomyolysis between 1990 and 1999 (Black and Jick 2002). Most information on the incidence of rhabdomyolysis has come from observational studies in users of statins, a drug class often co-prescribed in T2DM patients.

In a recent systematic review of cohort studies, the incidence of rhabdomyolysis in users of statins was reported to be 0.34 (95% CI 1.6-6.5) per 10,000 person-years among all statin users (except cerivastatin) (Law and Rudnicka 2006).

Similar results were found by Graham et al (2004) who estimated the risk of rhabdomyolysis in patients treated with lipid-lowering drugs (including statins) in the ambulatory setting. The incidence rate for rhabdomyolysis with statin monotherapy was about 0.44 per 10,000 person-years of therapy. This rate increased to about 6 per 10,000 person-years for combination therapy with a fibrate.

In the cohort study mentioned above by Nichols and Koro (2007) based on Kaiser Permanente Northwest data, the proportion of diabetic patients identified with rhabdomyolysis during follow-up was 0.12% (95% CI 0.05-0.18%) in those without and 0.13% (0.06-0.20%) in those with statin exposure. The corresponding adjusted incidence rates were 2 (95% CI 1-5) and 1 (95% CI 1-3) per 10,000 person-years, respectively in those without and with statin exposure.

The incidence of the most common statin-associated muscle-related complaint, i.e. non-specific muscle pain or joint pain in the absence of elevated CK, is approximately 5% (Christopher-Stine 2006).

Prevalence

The etiology of muscle-related events (e.g. myopathy, muscle infarction or pyomyositis) in the diabetic population includes conditions such as neuropathy, peripheral vascular disease, infections and certain concomitant medications, particularly statins. Neuropathy is a highly prevalent complication of diabetes which may be associated for instance with lower extremity proximal myopathy.

Hong et al (1998) assessed the significance of symptoms -suggestive of neuropathy in T2DM patients and non-diabetic controls matched for age and gender. More T2DM patients than controls experienced symptoms suggestive of lower extremity proximal myopathy (i.e. weakness climbing stairs: 42 vs. 19%, getting up from squatting position: 31 vs. 11%). Additionally, more T2DM patients than controls had weaker hip muscles (24 vs. 6%).

Diabetic muscle infarction is a rare, painful and potentially serious complication in patients with poorly controlled DM. It is frequently misdiagnosed clinically as abscess, neoplasm, or myositis. It can be triggered by an ischemic event and causes extensive muscle necrosis through hypoxia-reperfusion injury and compartment syndrome. CK levels may be normal or slightly increased.

	Only a few cases with diabetic muscle infarction have been published. Due to difficulties in making the correct diagnosis and excluding other etiologies, it can be speculated that diabetic muscle infarction is under-diagnosed (Sahin et al 2005). Another rare muscle-related event that may occur in diabetics is pyomyositis. It is a pyogenic infection of the skeletal muscle that can lead to abscess formation. It commonly occurs in the tropics, but is also recognized in temperate climates, with Human immunodeficiency virus (HIV) infection and diabetes being the main predisposing factors (Crum 2004, Seah et al 2004). Since 1981 more than 330 cases have been published. The most common underlying medical condition in HIV-negative patients was diabetes which was observed in 19% of cases (Crum 2004). Molsted et al (2012) estimated the prevalence of musculoskeletal pain in Danish 951 patients with T2DM aged 18+ years using a self-administered validated questionnaire to assess the history of pain in three parts in the musculoskeletal system during the past 14 days, i.e. pain in the shoulder and neck, low-back pain, and pain in the arm, hand, knee and/or hip. Patients with T2DM had a significantly higher prevalence of musculoskeletal pain in all three areas in the body (52% for shoulder and neck pain, 60% for low-back pain, 71% for pain in arm, hand, knee and/or hip) compared to an age- and gender-matched sample of the general population from the same geographical region The prevalence of musculoskeletal pain was 1.7- to 2.1-times ($p < 0.001$) higher in T2DM patients than the control patients. **Mortality** No information on mortality due to rhabdomyolysis or other muscle-related events in T2DM patients could be identified.
Risk factors and risk groups	Patients treated concomitantly with statins are at increased risk of myopathy. Statins can cause different degrees of myopathy, ultimately leading to rhabdomyolysis and acute renal failure.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.9 PL Section 4 **Additional risk minimization measures:** None.

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Galvus/Eucreas.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Liver Injury

Targeted Follow-up Checklist for Liver Injury (Jan 2016)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

1. Diagnosis and date of diagnosis_____

2. Did the patient present with any of the following signs or symptoms? Check all that apply:

☐ Jaundice☐ Ascites☐ Asterixis (flapping tremor)

☐ Dark urine☐ Fever☐ Altered mental status

☐ Pale stool☐ Fatigue☐ Abdominal pain (specify location)

☐ Pruritus☐ Bleeding (specify location)☐ Anorexia

☐ Nausea☐ Spider angiomata☐ Variceal Bleeding

☐ Caput medusa☐ Peripheral edema☐ Fetor hepaticus

☐ Gynecomastia☐ Muscle wasting☐ Other (specify)

☐ None

3. Were any of the following diagnostic tests performed?

►If yes, please specify the dates and results including reference range and pre- and post- treatment values:

☐ Liver function tests

☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus

☐ Autoantibody tests

☐ Abdominal or hepatobiliary ultrasound (with or without Doppler's)

☐ Abdominal CT scan

☐ Liver biopsy

☐ Liver transplant (planned or completed)

☐ Other (specify)

☐ None

4. Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details:

☐ Previously elevated liver enzymes☐ Tattoos

☐ Hepatitis☐ Transfusion or blood product administration

☐ Other hepatobiliary disease or dysfunction☐ Gilbert's disease

☐ Autoimmune disease (specify type)☐ Alcohol intake (quantify if possible)☐ Active or chronic pancreatitis☐ Drug abuse

☐ Diabetes mellitus (Type I or II)☐ Foreign travel

☐ Non-alcoholic steatohepatitis☐ Active gall bladder disease

☐Cirrhosis☐ Portal hypertension

☐Ascites☐ Variceal bleeding/esophageal varices☐ Spider angiomata☐ Thrombocytopenia

☐ None ☐ Other (specify)

5. Has the patient recently (i.e. within the past 6 months) taken any of the following? Check all that apply:

☐ Sulfonamides☐ Furosemide☐ ACE Inhibitors

☐ Valproic acid☐ NSAIDS (e.g. ibuprofen) ☐ Estrogens (oral contraceptives)☐ Metronidazole☐ Acetaminophen/Paracetamol☐ Amiodarone

☐ COX II inhibitors(e.g. celecoxib)☐ Tetracycline☐ Steroids

☐ Thiazide diuretics☐ 6-Mercaptopurine☐ Statins

☐ Nicotinic acid☐ Methotrexate☐ Other (specify)

☐ None

Targeted Follow-up Checklist for

Pancreatitis and Amylase & Lipase Elevations (version 2, 2016)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply:**

☐ Upper abdominal pain ☐ Indigestion

☐ Swollen and tender abdomen☐ Weight loss

☐ Nausea and vomiting☐ Steatorrhea

☐ Fever☐ Dehydration

☐ Clammy skin☐ Diarrhea

☐ Hypotension☐ Bloating

☐ Jaundice☐ Radiation of pain to back/flank

☐ Cullen's sign ☐ Tachycardia

☐ Reduced bowel sounds

☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and specify including dates and results:**

☐ Abdominal ultrasound☐ None of the above

☐ CT scan

☐ Amylase and Lipase

☐ Abdominal MRI

☐ Any additional blood test abnormalities **(specify):**

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Gallstones ☐ Hyperparathyroidism

☐ Heavy alcohol use ☐ Hypertriglyceridemia

☐ Other gallbladder (biliary disease) ☐ Cystic Fibrosis

☐ Pancreatic or common bile duct surgical procedures ☐ Cigarette smoking

☐ Traumatic Injury ☐ Viral infections

☐ Pancreatic cancer ☐ Other relevant history *(please specify)*

☐ Hypercalcemia ☐ Abdominal surgery

☐ Endoscopic retrograde cholangiopancreatography (ERCP) ☐ Family history of pancreatitis

☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply:**

☐ Estrogens☐ Corticosteroids

☐ Thiazide diuretics☐ Azathioprine

Lactic Acidosis

Galvus/Eucreas targeted follow-up checklist (v1.1, Mar 2017)

Targeted Follow-up Checklist

Lactic acidosis with vildagliptin/metformin FDC

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Information on daily dose of vildagliptin/metformin FDC:

Medicinal product		**Average daily dose (mg/day)**	**Dose level at last date taken**	**Time of last dose**	**Plasma Level (metformin) if done/date**	**Concentration in erythrocyte (metformin) if done/ date**

	Start Date	Last date drug taken					
Vildagliptin/metformin FDC							
Total Metformin ***(including concomitant additional metformin)***							

Event Description

For this adverse event, did the patient present with any of the following signs or symptoms? **Check all that apply**

☐Arrhythmias	☐Hypotension	☐Chest pain	☐Deep rapid breathing	☐Acidotic dyspnea
☐Altered mental status	☐Decreased visual acuity	☐Coma	☐Seizure	☐Nausea
☐Vomiting	☐Diarrhea	☐Abdominal pain	☐Bone pain	☐Muscle wasting/weakness
☐Muscle cramps	☐Asthenia	☐Hypothermia	☐None of the above	☐Other *(please specify)*

Diagnostic/Laboratory tests:

Were any of the following diagnostic tests performed for this adverse event? **Check all that apply**.
(Please specify tests, dates, results. For all laboratory results, please specify units)

Name	Values before the event (dd/mm/yyyy)	Unit / Reference Range	Values during the event (dd/mm/yyyy)	Unit / Reference Range	Follow-up measurement (dd/mm/yyyy)	Unit / Reference Range
Blood pH						
Bicarbonate						
Plasma lactate level						
Anion gap						
Urinary ketones						
β-hydroxybutyrate						
$[Na^+]$						
$[K^+]$						
$[Cl^-]$						
$[HCO_3^-]$						
eGFR						
Blood creatinine						
Blood BUN						

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

☐Excessive alcohol use
☐Exposure to contrast media
☐Infection/sepsis
☐Renal disease
☐Diarrhea/vomiting
☐Dehydration
☐Malnutrition
☐Acute heart failure
☐Acute myocardial infarction
☐Other conditions with hypoxia

Further details (e.g. date of onset etc.)

Concomitant medications

Please list concomitant drugs being taken by the patient at the time of the event
(***Please specify drug, indication,dose, route, date and duration)***

Drug	Indication	Dose & Route	Date & Duration

Treatment of lactic acidosis

Please list the relevant treatments for the adverse event
(Please specify relevant treatment[s], dates and outcomes)

Treatment	Dates	Outcome

Myopathies including Rhabdomyolysis

Targeted Follow-up Checklist

Myopathies including Rhabdomyolysis (Sep 2015)

Targeted Follow-up Checklist
Myopathies including Rhabdomyolysis

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms? Check all that apply
☐ Muscle tenderness☐ Walking difficulty☐ Fatigue
☐ Muscle stiffness☐ Respiratory difficulty☐ Acute renal failure
☐ Muscle aching (myalgia)☐ Dark or red color urine☐ Disseminated
☐ Muscle weakness☐ General weaknessintravascular coagulation
☐ Muscle spasms☐ Frequent falls☐ Compartment syndrome
☐ Muscle hypotonicity☐ Poor balance☐ Thyroid disorder (hypo/
☐ Muscle hypertonicity☐ Joint painhyperthyroidism
☐ Muscle swelling☐ None of the above

Were abnormalities detected in any of the following diagnostic tests? Check all that apply and please specify which test(s), dates and results
☐ Electrolyte levels (i.e. hyperkalemia, hypocalcaemia)
☐ CPK, myoglobin, aldolase, albumin (hypoalbuminemia)
☐ Urinalysis including casts, hemoglobin, myoglobin
☐ Renal tests indicating renal insufficiency (Serum creatinine, BUN)
☐ Muscle biopsy
☐ None of the above

Patient History:

Had the patient been exposed to hazardous toxins in the past? ☐ Yes (please describe) ☐ No ☐ Unknown

Does the patient have evidence of any of the following? Check all that apply
☐ Metabolic or genetic disorders (e.g. disorders of muscle☐ Exertional rhabdomyolysis carbohydrate metabolism, carnitine palmitoyltransferase☐ Crush injury or trauma deficiency)☐ Alcoholism or alcohol abuse (please specify)
☐ Hypothermia☐ Drug or substance abuse (please specify)
☐ Malignant hyperthermia☐ Electrical injuries
☐ Neuroleptic malignant syndrome☐ Viral infection (e.g. EBV, CMV, HIV, Herpes virus)
☐ Hyperthermia☐ Endocrine abnormality (e.g. diabetic ketoacidosis)
☐ Bacterial infection☐Seizures/Epilepsy
☐ Genetic abnormality (e.g. hereditary metabolic abnormality)☐ Arterial thrombosis
☐ Snake or insect envenomation (please specify)☐ None of the above

Has the patient recently taken any of the following? Check all that apply
☐ HMG-CoA reductase inhibitors (statins)☐ Nucleoside reverse transcriptase inhibitors (NRTIs)
☐ Gemfibrozil ☐ Corticosteroids
☐ Niacin☐ Injection of iron-dextran
☐ Cyclosporine☐ Erythromycin
☐ Itraconazole☐ Neuroleptics (phenothiazines)
☐ MAOIs (esp. in combination with SSRIs, lithium,☐ SSRIs/SNRIs tri-cyclic antidepressants)☐ Colchicine
☐ D-penicillamine☐ Chloroquine
☐ Hydroxychloroquine☐ None of the above

Was there any evidence of drug-drug-interactions leading up to this event?
☐ Yes (please specify, including medications) ☐ No ☐ Unknown

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.