EU RISK MANAGEMENT PLAN (RMP) FOR

Sitagliptin phosphate/ Metformin hydrochloride

RMP version to be assessed as part of this application:

RMP Version number: 10.1

Data lock point for this RMP: 30-Jun-2020

Date of finalization: 29-JUL-2020

Rationale for submitting an updated RMP:

This RMP was updated to include clinical trial exposure to sitagliptin (+) metformin in patients 10-17 years of age.

Summary of significant changes in this RMP:

RMP Section	UPDATE INFORMATION
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Updated due to the new release of IDF Diabetes Atlas and CDC Diabetes Report.
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE	Added Table SIII.2.7: Clinical Trial Exposure to Sitagliptin in Patients 10-17 years of Age.
PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS	Deleted Patients below 18 years of age from Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs.
PART II: MODULE SV - Post-authorization Experience	Updated patient exposure data

Other RMP versions under evaluation:

There are no previously-submitted versions of this RMP that are still under evaluation by the Agency.

Details of the currently approved RMP:

Version number: 10.0

Approved with procedure: WS1357

Date of approval (opinion date): 29-Nov-2018

QPPV name: Guy Demol, MD

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

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily

QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	sitagliptin phosphate / metformin hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	A10BD07
Marketing Authorisation Holder or Applicant	MAH Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands Applicant Merck Sharp & Dohme (Europe) Inc. 5 Clos du Lynx B-1200 Brussels, Belgium
Number of medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	Janumet/Velmetia/Efficib/Ristfor
Marketing authorisation procedure	Centralized procedure
Brief description of the product	**Chemical class:** Dipeptidyl peptidase IV (DPP-4) inhibitor / Biguanide combination
	Summary of mode of action: Fixed-dose combination product containing two antihyperglycaemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a DPP-4 inhibitor, and metformin hydrochloride, a member of the biguanide class.
	Important information about its composition: Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 or 1000 mg of metformin hydrochloride.
Hyperlink to the Prescribing Information	Updated product information for sitagliptin/metformin FDC is not included within this procedure, hence reference is made to the latest-approved product information residing in module 1.3, eCTD sequence 0198, as approved under procedure WS1803.

Table Part I.1: Product Overview

Indication(s) in the EEA	Current: For adult patients with type 2 diabetes mellitus: Sitagliptin/metformin fixed dose combination (FDC) is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. Sitagliptin/metformin FDC is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. Sitagliptin/metformin FDC is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. Sitagliptin/metformin FDC is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dosage of insulin and metformin alone do not provide adequate glycaemic control.
Dosage in the EEA	Current: The dose of antihyperglycaemic therapy with Janumet should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin. For patients switching from co-administration of sitagliptin and metformin, Janumet should be initiated at the dose of sitagliptin and metformin already being taken. For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea, the dose of Janumet should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Janumet is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist, the dose of Janumet should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. <u>Renal Impairment:</u> For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin, the dose of Janumet should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Janumet is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia. No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 mL/min). A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the

Table Part I.1: Product Overview

<table>
<tr><td></td><td>elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Janumet is available, individual monocomponents should be used instead of the fixed-dose combination.

<table>
<tr><th>GFR mL/min</th><th>Metformin</th><th>Sitagliptin</th></tr>
<tr><td>60-89</td><td>Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.</td><td>Maximum daily dose is 100 mg.</td></tr>
<tr><td>45-59</td><td>Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.</td><td>Maximum daily dose is 100 mg.</td></tr>
<tr><td>30-44</td><td>Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.</td><td>Maximum daily dose is 50 mg.</td></tr>
<tr><td><30</td><td>Metformin is contraindicated</td><td>Maximum daily dose is 25 mg.</td></tr>
</table>
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current (if applicable): Film-coated tablet
50/850 and 50/1000 dose strengths are approved and marketed in the European Union (EU).</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: For adult patients with type 2 diabetes mellitus (T2DM) in adjunct to diet, exercise and other therapies.

Incidence:

The number of adults with newly diagnosed T2DM is increasing. In the United States (US), the number of incident cases among adults, age 18-79 years, has more than tripled over the past several decades, increasing from 493,000 in 1980 to more than 1.5 million in 2018 [Ref. 5.4: 04DQ3X],[Ref. 5.4: 05HY26]. The incidence rate of diagnosed diabetes was 6.9 per 1000 persons in US adults aged 18 or older in 2018 [Ref. 5.4: 04Y8C8]. Compared to adults aged 18 to 44 years, incidence rates of diagnosed diabetes were higher among adults aged 45 to 64 years and those aged 65 years and older (4.3 per 1,000 in adults aged 18-44 years, 9.9 per 1,000 in adults aged 45-64 years, and 8.8 per 1,000 in adults aged 65 years or older) [Ref. 5.4: 05HY26].The incidence was similar between men and women [Ref. 5.4: 05HY26]. In the United Kingdom (UK), the crude incidence rate of T2DM has increased from 169 per 100,000 in 1991 to 515 per 100,000 in 2010. The incidence was higher in men (536 per 100,000) versus women (495 per 100,000), and it also increased with age, with the highest incidence rate seen in 70-79 age groups at 1,486 per 100,000. [Ref. 5.4: 03RTYQ]

Prevalence:

An estimated 463 million adults worldwide, representing 9.3% of adults 20-79 years, had diabetes in 2019. By 2030 a projected 578 million, and by 2045, 700 million adults aged 20–79 years, will have diabetes. In Europe, an estimated 59.3 million (8.9%) adults aged 20-79 years have diabetes. The prevalence proportions were 7.6% in France, 15.3% in Germany, 8.3% in Italy, 10.5% in Spain and 5.6% in UK. [Ref. 5.4: 05JV08]

Demographics of the population with T2DM and risk factors for the disease:

Diabetes estimates for 2019 show a typically increasing prevalence of diabetes by age. Similar trends are predicted for the years 2030 and 2045. Prevalence is lowest among adults aged 20–24 years (1.4% in 2019). Among adults aged 75–79 years 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. [Ref. 5.4: 05JV08]

The prevalence of diabetes for women 20-79 years is estimated to be 9.0% which is slightly lower than among men (9.6%). The diabetes prevalence is expected to increase to 10.8% in women and to 11.1% in men in 2045 [Ref. 5.4: 05JV08].

In the US, prevalence of diagnosed diabetes was higher among American Indians/Alaska Natives (14.7%), people of Hispanic ethnicity (12.5%), and non-Hispanic blacks (11.7%),

than among Asians (8.2%) and non-Hispanic whites (7.5%) [Ref. 5.4: 05HY26]. The distribution of self-reported race in the UK Prospective Diabetes Study (UKPDS) was 82% White, 10% Asian Indian, and 8% Afro-Caribbean [Ref. 5.4: 03Q3XC].

Common risk factors for T2DM include increasing age, smoking, hypertension, being overweight or obese, physical inactivity, family history of T2DM, race/ethnicity (e.g. African American, Latino, Native American, Asian American, and Pacific islander), impaired glucose metabolism ("prediabetes"), and gestational diabetes [Ref. 5.4: 03TPR6, 03RRZ9, 043NNR].

The main existing treatment options:

Current pharmacologic treatment of T2DM includes several classes of glucose-lowering agents [Ref. 5.4: 05HGYT]:

• Metformin (Biguanides);

• Sulfonylureas (SUs);

• Dipeptidyl peptidase-4 (DPP-4) inhibitors;

• Sodium-glucose co-transporter-2 (SGLT-2) inhibitors;

• Meglitinides;

• Alpha-glucosidase inhibitors;

• Thiazolidinediones (TZDs);

• Dopamine agonist (ie, bromocriptine);

• Bile acid sequestrant (ie, colesevelam);

• Glucagon-like peptide-1 (GLP-1) receptor agonists;

• Amylin-mimetics;

• Insulin and insulin analogues.

Current guidelines from the European Association for the Study of Diabetes and the American Diabetes Association recommend a stepwise and individualized treatment approach [Ref. 5.4: 05HGYT],[Ref. 5.4: 05JSPF]. The guidelines recommend metformin as the first-line antihyperglycemic medication, unless the patient cannot tolerate it or it is contraindicated. If, after approximately 3 months, the glycosylated hemoglobin A1c (A1C) target is not achieved, therapy should be augmented to a 2-drug combination followed by the addition of other glucose lowering agents approximately every 3 months if A1C goal is still not achieved.

Natural history of the indicated condition in the T2DM population, including mortality and morbidity:

T2DM, the predominant type of diabetes accounting for >90% of all diabetes, is a progressive disease involving three key defects: insulin resistance; insulin secretory dysfunction; and hepatic glucose overproduction [Ref. 5.4: 03Q3X2]. Glucose disposal into insulin-sensitive tissues in response to insulin defines insulin sensitivity. Insulin resistance (loss of insulin sensitivity) and consequent hyperinsulinemia are early stages in the pathophysiology of T2DM. Progressive weight gain and obesity are potent inducers of insulin resistance. Insulin secretion by pancreatic beta cells progressively declines, with decomposition of the beta cells. Overproduction of glucose by the liver is the third pathogenic feature. Increased hepatic insulin resistance, beta cell dysfunction, and hyperglucagonemia contribute to hepatic glucose overproduction, primarily by altering rates of glucose uptake, glycogenolysis, and gluconeogenesis in the liver [Ref. 5.4: 03R2DJ], [Ref. 5.4: 03R2DK].

Hyperglycemia can cause both microvascular complications including nephropathy, neuropathy, and retinopathy, and macrovascular complications including coronary artery disease (CAD) leading to angina or myocardial infarction, peripheral artery disease (PAD) contributing to stroke, diabetic encephalopathy and diabetic foot [Ref. 5.4: 043NNR] [Ref. 5.4: 04XV7S].

Microvascular complications:

Chronic kidney disease (CKD) among patients with diabetes can be true diabetic nephropathy, but can also be caused indirectly by diabetes due mostly to hypertension, but also polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections or macrovascular angiopathy. Based on data from the UK, one-fifth of people with diabetes will develop chronic kidney disease [Ref. 5.4: 04XV7S].

Diabetic neuropathy is an impairment of normal activities of the nerves throughout the body and can alter autonomic, motor and sensory functions. The reported prevalence of diabetic peripheral neuropathy ranges from 16% to as high as 66% [Ref. 5.4: 04XV7S].

Diabetic retinopathy is the leading cause of vision loss in working-age adults (20 to 65 years) and approximately one in three people living with diabetes have some degree of diabetic retinopathy and one in ten will develop a vision threatening form of the disease. The prevalence of any retinopathy in persons with diabetes is 35% while proliferative retinopathy is 7% [Ref. 5.4: 04XV7S].

Macrovascular complications:

People with diabetes are at increased risk of cardiovascular disease (CVD). Diabetes is also associated with high blood pressure and cholesterol levels, which lead to increased risk of cardiovascular complications such as angina, coronary artery disease (CAD), myocardial infarction, stroke, peripheral arterial disease (PAD), and congestive heart failure. Overall, it is estimated that every year 14 to 47 per 1,000 middle-aged people with diabetes (50-69

years) living in high and middle income countries have a CVD event. Among these, 2-26 per 1,000 are coronary artery disease events, and 2-18 per 1,000 are strokes [Ref. 5.4: 04XV7S].

Diabetic foot is another severe chronic complication, and it consists of lesions in the deep tissues associated with neurological disorders and peripheral vascular disease in the lower limbs. In high income countries, the annual incidence of foot ulceration among people with diabetes is about 2%, being the most common cause of non-traumatic amputation, approximately 1% of people with diabetes suffer lower-limb amputation [Ref. 5.4: 04XV7S].

As for mortality, the World Health Organization (WHO) reports that hyperglycemia is the third highest risk factor for premature mortality, after high blood pressure and tobacco use [Ref. 5.4: 04F7LB]. In the United States, diabetes was the seventh leading cause of death in 2017 [Ref. 5.4: 05HY26]. Worldwide, approximately 4.2 million people aged between 20 and 79 years died from diabetes in 2019, accounting for 11.3% of global all-cause mortality among people in this age group. In the USA, more than 188,969 people died from diabetes in 2019, one of the highest numbers of deaths due to diabetes of any country in the world. In Europe, diabetes contributed to 465,900 of the deaths among adults aged 20-79 years, with 18,656 deaths in France, 50,096 in Germany, 15,656 in Italy, 15,394 deaths in Spain and 13,951 in UK among adults aged 20-79 years, according to IDF 2019 report.
[Ref. 5.4: 05JV08]

Important co-morbidities:

Besides diabetes-related complications discussed in the previous section, common comorbidities observed in patients with diabetes are listed below: [Ref. 5.4: 05HGYT]

- Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder.
- Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia.
- Diabetes is associated with the development of nonalcoholic chronic liver disease and with hepatocellular carcinoma.
- People with diabetes are at an approximately two-fold higher risk of developing acute pancreatitis.
- Age-specific hip fracture risk is significantly increased in people with diabetes in both sexes.
- Hearing impairment, both in high frequency and low/mid-frequency ranges, is more common in people with diabetes than in those without, perhaps due to neuropathy and/or vascular disease.
- Prevalence of clinically significant psychopathology diagnoses is considerably more common in people with diabetes than in those without the disease.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1: Summary of Important Safety Findings from Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
SITAGLIPTIN	
Genotoxicity/Carcinogenicity	
Sitagliptin was not genotoxic in vitro or in vivo in a battery of assays to detect mutagenicity, direct DNA damage, or clastogenicity. The carcinogenic potential of sitagliptin was determined in mice at doses of 50, 125, 250, and 500 mg/kg/day for 2 years. Sitagliptin was not carcinogenic in mice at a dose up to 500 mg/kg/day. The carcinogenic potential in rats was assessed at doses of 50, 150, and 500 mg/kg/day for 2 years. Sitagliptin increased the incidence of hepatic tumors in rats dosed with 500 mg/kg/day, a maximum tolerated dose in rats which produces chronic liver injury. This finding was considered secondary to the chronic liver injury observed in rats at 500 mg/kg/day. Data reported in the literature suggests that DPP-4 may be involved in the regression of the malignant phenotype in cancer cells, and that the transformation of normal cells to cancer cells may be accompanied by a loss of DPP-4 expression. Currently, it seems that these effects occur independently of the enzyme activity of DPP-4, as in several experiments it was shown that the effects were also achieved with inactive DPP-4. It therefore seems that, combined with the results of the 2-year carcinogenicity studies, as yet there are no indications for an increased carcinogenic risk associated with inhibition of DPP-4 enzyme activity.	Due to sitagliptin being non-genotoxic, the fact that there was a sufficiently high safety margin for the hepatic tumors, and that the increased incidence of hepatic tumors was considered secondary to the chronic liver injury in rats at 500 mg/kg/day, as well as the fact that hepatotoxicity was not observed in clinical studies at doses providing systemic exposure 8-fold that following the recommended dose of 100 mg/day, this increase in hepatic tumors is not considered relevant to humans. There was no increase in the incidence of tumors in any other tissues in the rat carcinogenicity study.
Pancreatitis	
Pancreatitis has been raised as a potential issue with DPP-4 and GLP-1 compounds for the treatment of type 2 diabetes. To address this issue, preclinical toxicity studies in mice, rats, dogs, and monkeys were reviewed for evidence of pancreatitis. There was no evidence of sitagliptin-related pancreatitis observed. To address the potential issue of an increase in susceptibility to pancreatitis in diabetic animals, H&E slides of the pancreas from a high fat diet/streptozotocin (HFD/ STZ) mouse model of diabetes were evaluated for pancreatitis and ductal proliferation. The HFD/STZ mice were dosed with up to 840 mg/kg/day of sitagliptin for 10 weeks, with no sitagliptin-related pancreatic changes. In addition, in a 1 year study in hIAPP transgenic mice (a transgenic mouse expressing human islet amyloid polypeptide [hIAPP] under the rat insulin-2 gene promoter fragment and characterized by glucose intolerance and hyperglycemia) (a model similar to the transgenic rodent model of diabetes used by Matveyenko et al. (2009) [Ref. 5.4: 03TNK2], and the only hIAPP transgenic rodent model available for use by the public at the time of this study), evaluation of H&E stained pancreata showed no	The H&E stained pancreas from the HFD/STZ mouse model of diabetes shows no evidence of sitagliptin-related changes (pancreatitis or changes in ductal proliferation). In a 1 year study in hIAPP transgenic mice and a 3 month study in ZDF rats, no test-article related pancreatitis or increase in pancreatic ductal cell proliferation were observed. There is no preclinical or clinical signal for pancreatitis or pancreatic cancer.

Table SII.1: Summary of Important Safety Findings from Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
sitagliptin-related changes. Ductal proliferation was increased in sitagliptin, metformin and sitagliptin + metformin groups compared to untreated hIAPP mice, but was equivalent to that in wild type controls. No pancreatic ductal abnormalities were observed in any group [Ref. 5.4: 03RLWN]. However, the hIAPP mice from this study were euglycemic and not hyperglycemic as were the hIAPP rats used by Matveyenko et al. (2009) [Ref. 5.4: 03TNK2]. To address this concern an additional 3 month study with sitagliptin and metformin has been conducted using the Zucker diabetic fatty (ZDF) rat model of diabetes; these animals are clearly hyperglycemic. In this study the pancreas was evaluated for evidence of pancreatitis and a quantitative evaluation of ductal cell proliferation was conducted. There was no evidence of pancreatitis or increase in ductal cell proliferation in this study. In a publication by Chadwick et al. (2013) [Ref. 5.4: 03TVF0] the authors conclude that the recent publications raising concerns about pancreatitis and pancreatic cancer attributed to incretin therapies are background findings and independent of drug, diet, or glycemic status.	
METFORMIN	
Lactic Acidosis	
Lactic acidosis was observed in dogs administered 50 mg/kg/day of metformin.	Lactic acidosis in humans is a rare adverse event observed with metformin, and is addressed in metformin and sitagliptin/ metformin fixed-dose combination product labels.
SITAGLIPTIN + METFORMIN	
None	

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief Overview of Development

Sitagliptin/metformin FDC was originally approved with the following indication: For adult patients with type 2 diabetes mellitus:

Sitagliptin/metformin FDC is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Sitagliptin/metformin FDC is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

After its initial approval, sitagliptin/metformin FDC was also approved for the following indications:

1. Sitagliptin/metformin FDC is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control. (This indication was supported by the results of study P051, a 24-week phase III, multicenter, randomized, double-blind clinical trial to study the safety and efficacy of sitagliptin in patients with type 2 diabetes mellitus who have inadequate glycaemic control on insulin therapy (alone or in combination with metformin). The proportion of patients using metformin in this study was 72%.
2. Sitagliptin/metformin FDC is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. (This indication was supported by the results of a 54-weeks efficacy and safety study (P052). This was a Phase III clinical study designed to assess the glycaemic efficacy and tolerability of sitagliptin added to the combination of metformin and rosiglitazone compared with placebo in patients with inadequate glycaemic control on dual combination therapy.)

SIII.2 Completed Clinical Research Studies as of 30 June 2013

The clinical research development program to support the sitagliptin/metformin FDC for the treatment of patients with T2DM in adults includes 18 Phase II/III studies completed as of 30-Jun-2013 (see Table SIII.2.1). This group of studies includes patients receiving sitagliptin 100 mg/day (100 mg q.d. or 50 mg b.i.d.) in combination with metformin at varying dose strengths throughout the study treatment period. For patients in this group of studies, exposure to sitagliptin/metformin includes data collected prior to and after initiation of rescue therapy. Across these 18 studies, 5036 patients were exposed to co-administration of sitagliptin and metformin or the sitagliptin/metformin FDC. The mean duration of exposure to sitagliptin/metformin (any dose) was 292.3 days, with a cumulative exposure of 4030.7

patient-years. Details of the exposure to sitagliptin/metformin by study, duration, dose, age and gender, race, and special populations are shown below in Table SIII.2.2 through Table SIII.2.6.

Data from the Japanese studies reside in separate databases and were not included in the analysis below. Results from the Phase II/III Japanese studies are generally consistent with results from the studies included in Table SIII.2.1 below.

Exposure data from the cardiovascular outcomes trial (TECOS), which completed in 2015, can be found in Section SIII.3.

Table SIII.2.1: Clinical Trial Exposure to Both Sitagliptin and Metformin by Study:
June 2013 Sitagliptin in Combination with Metformin Population, Including Data After Initiation of Glycemic Rescue Therapy

Population	Subjects	Mean Duration (days)	Subject Time (years)
Protocol 015	28	28.3	2.2
Protocol 020	464	503.6	639.8
Protocol 024	588	483.4	778.3
Protocol 035	116	294.9	93.7
Protocol 036 Blinded Cohort	372	535.1	545.0
Protocol 036 OLC	117	142.3	45.6
Protocol 051	229	161.2	101.1
Protocol 052	170	347.7	161.8
Protocol 053	96	194.0	51.0
Protocol 066	261	199.7	142.7
Protocol 068	222	263.1	159.9
Protocol 074	197	157.1	84.7
Protocol 079	626	230.2	394.6
Protocol 121	247	152.5	103.1
Protocol 128	157	176.2	75.7
Protocol 229	210	339.6	195.3
Protocol 403	326	163.6	146.1
Protocol 801	94	117.5	30.2
Protocol 803	516	198.1	279.8
Total	5036	292.3	4030.7

OLC = open label cohort

Table SIII.2.2: Clinical Trial Exposure to Both Sitagliptin and Metformin by Duration: June 2013 Sitagliptin in Combination with Metformin Population, Including Data After Initiation of Glycemic Rescue Therapy

Duration of Exposure	Subjects	Subject Time (years)
> 0 days	5036	4030.7
> 1 month (4 weeks)	4847	4024.5
> 3 months (12 weeks)	4624	3991.6
> 6 months (24 weeks)	3898	3708.8
> 12 months (48 weeks)	1422	2188.5
> 18 months (72 weeks)	791	1512.2
Each subject is counted once on each applicable duration category row.		

Table SIII.2.3: Clinical Trial Exposure to Sitagliptin in Combination Studies with Metformin by Dose: June 2013 Sitagliptin in Combination with Metformin Population, Including Data After Initiation of Glycemic Rescue Therapy

Dose of Exposure	Subjects	Mean Duration (days)	Subject Time (years)
Any dose	5036	292.3	4030.7
50 mg	1314	10.1	36.2
100 mg	5008	291.0	3989.6
150 mg	177	4.7	2.3
200 mg	180	5.2	2.5
>200 mg	1	20.0	0.1
Each subject is counted once on each applicable dose category row.			

Table SIII.2.4: Clinical Trial Exposure to Both Sitagliptin and Metformin by Age: Category and Gender June 2013 Sitagliptin in Combination with Metformin Population, Including Data After Initiation of Glycemic Rescue Therapy

Age Category	Subjects			Mean Duration (days)			Subject Time (years)		
(years)	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	2323	1927	4250	290.4	297.0	293.4	1846.9	1566.8	3413.7
≥65	434	352	786	299.3	271.2	286.7	355.6	261.4	617.0
Total	2757	2279	5036	291.8	293.0	292.3	2202.5	1828.1	4030.7

Table SIII.2.5: Clinical Trial Exposure to Both Sitagliptin and Metformin by Race: June 2013 Sitagliptin in Combination with Metformin Population, Including Data After Initiation of Glycemic Rescue Therapy

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	122	219.1	73.2
Asian	1091	238.3	711.7
Black Or African American	252	295.4	203.8
Multi-Racial	280	288.8	221.4
Native Hawaiian Or Other Pacific Islander	15	279.1	11.5
Unknown	340	384.3	357.8
White	2935	305.0	2450.9
NULL	1	124.0	0.3
Total	5036	292.3	4030.7

Race is classified as unknown for patients whose reported race was Hispanic. These patients come from studies (020, 024, 035, 036, 052, 053) in which ethnicity data were not collected separately from race.
Race is classified as null for one patient whose race datum is missing.

Table SIII.2.6: Clinical Trial Exposure to Sitagliptin by Special Population: June 2013 Sitagliptin Population, Including Data After Initiation of Glycemic Rescue Therapy

Population	Subjects	Mean Duration (days)	Subject Time (years)
Renal impairment (baseline serum creatinine >ULN)*	338	288.8	267.3
Hepatic impairment (baseline ALT>ULN or AST>ULN)	2335	297.7	1903.2
Cardiac impairment (any cardiac SOC medical history)	1491	312.8	1276.9

A subject is counted for each applicable population.
* Subject population included mild to severe renal impairment, including ESRD.

Table SIII.2.7: Clinical Trial Exposure to Sitagliptin in Patients 10-17 years of Age

Population	Subjects	Mean Duration (days)	Subject Time (years)
Protocol 170*-W0-20	62	133.4	22.6
Protocol 170 W0-54[1]	28	348.8	26.7
Protocol 289**-W0-20	45	127.8	15.7
Protocol 289-W0-54[2]	42	335.0	38.5

* To evaluate the safety of fixed dose combinations (FDC) of sitagliptin and metformin in patients 10-17 years of age (inclusive). Sitagliptin/metformin FDC immediate release tablet
** To evaluate the safety of fixed dose combinations (FDC) of sitagliptin and metformin in patients 10-17 years of age (inclusive). Sitagliptin/metformin FDC extended release tablet
[1] Subject exposure through Week 0-54 for the subset who entered the extension study
[2] Subject exposure through Week 0-54 for the subset who entered Phase B

Treatment with sitagliptin as add on to metformin IR or XR did not provide clinically meaningful improvement in glycemic control in pediatric patients (10 to 17 years old) with T2DM, therefore it is not indicated for use in this population.

SIII.3 P082 (TECOS)

P082 (TECOS: A Randomized, Placebo-Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control) was a Phase III, multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. The first patient's first visit was on 16 December 2008, and the last-data-available date was 30 March 2015.

Eligible patients had T2DM and HbA1c ≥6.5% (48 mmol/mol) and ≤8.0% (64 mmol/mol) with stable doses of either monotherapy or dual combination therapy with metformin, pioglitazone, or a sulfonylurea, or, after a protocol amendment, with stable doses of insulin (i.e. ±20% of the scheduled total daily insulin dose), alone or in combination with metformin, for at least 3 months (i.e. no adjustments to oral antihyperglycemic therapy in the past 3 months). In addition, patients were at least 50 years of age, with preexisting documented vascular disease in coronary, cerebral, or peripheral arteries.

Baseline demographics were well-balanced between the treatment groups. Mean age at randomization was 65.4 years in the sitagliptin group and 65.5 years in the placebo group; 71% of patients in both groups were male. The treatment groups were well balanced at baseline with regard to duration of diabetes (mean 11.6 years in both groups), history of diabetes complications, antihyperglycemic agents (>80% taking metformin and approximately 45% taking a sulfonylurea in both groups), and HbA1c (mean and median 7.2% in both groups). Within the sitagliptin group and the placebo group, respectively, 74% and 75% had coronary artery disease, 25% and 24% had cerebrovascular disease, and 17% of patients in both treatment groups had pre-existing peripheral artery disease. The two treatment groups had similar rates of use across different classes of medication. In both treatment groups, mean estimated glomerular filtration rate at baseline was 75 mL/min/1.73m^2.

A total of 14,735 patients were randomly allocated to treatment either with sitagliptin once daily or placebo in a 1:1 ratio; of these, 14,671 were included in the intent to treat (ITT) population and 14,540 were included in the population of all patients as treated (APaT). For patients with estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2, the starting dose of sitagliptin or placebo was 100 mg q.d.; for patients with eGFR 30 to <50 mL/min/1.73 m^2, the starting dose of sitagliptin or matching placebo was 50 mg q.d.

For the APaT population, in the sitagliptin group (n = 7266) and in the placebo group (n = 7274) the mean (SD) duration of treatment was 31.7 months (14.2) and 31.0 months (14.6), respectively; and the median (Q1, Q3) duration of treatment was 32.0 months (24.5, 41.7) and 30.9 months (24.2, 41.2). The minimum duration of treatment was 0 months in both groups; the maximum duration was 67 months and 65 months, respectively.

Exposure to sitagliptin by treatment duration, age, gender and race in P082 is shown in Table SIII.3.1 through SIII.3.3.

Table SIII.3.1: Clinical Trial Exposure to Sitagliptin by Duration: P082 (All Patients as Treated)

Duration of Exposure	Sitagliptin (N=7266)
<4 months	407 (5.6%)
≥4 months-<8 months	252 (3.5%)
≥8 months-<12 months	206 (2.8%)
≥12 months-<18 months	267 (3.7%)
≥18 months-<24 months	351 (4.8%)
≥24 months-<30 months	1784 (24.6%)
≥30 months-<36 months	1091 (15.0%)
≥36 months-<42 months	1148 (15.8%)
≥42 months-<48 months	746 (10.3%)
≥48 months	1014 (14.0%)

Table SIII.3.2: Clinical Trial Exposure to Sitagliptin by Race: P082 (All Patients as Treated)

Race	n	Mean Duration (days)	Subject Time (years)
American Indian or Alaska Native	36	826.4	81.5
Asian	1,639	949.9	4,262.4
Black or African American	205	882.6	495.4
Native Hawaiian or Other Pacific Islander	5	1,309.6	17.9
White	4,908	892.7	11,995.0
Other[1]	473	867.3	1,123.2
Total	7,266	903.6	17,975.3

Table SIII.3.3: Clinical Trial Exposure to Sitagliptin by Age Category and Gender: P082 (All Patients as Treated)

	Sex		
Age Category (years)	Male	Female	Total
<65			
n	2,384	906	3,290
Mean duration (days)	941.4	918.3	935.1
Subject time (years)	6,144.9	2,277.8	8,422.7
≥65			
n	2,685	1,136	3,821
Mean duration (days)	875.5	854.7	869.3
Subject time (years)	6,436.0	2,658.4	9,094.4
Total[1]			

Table SIII.3.3: Clinical Trial Exposure to Sitagliptin by Age Category and Gender: P082 (All Patients as Treated)

	Sex		
Age Category (years)	**Male**	**Female**	**Total**
n	5,156	2,110	7,266
Mean duration (days)	909.3	889.7	903.6
Subject time (years)	12,835.4	5,139.8	17,975.3

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
History of type 1 diabetes mellitus	The mechanism of action of sitagliptin precludes its being an effective antihyperglycemic agent in patients with type 1 diabetes mellitus.	No	The sitagliptin EU SmPC clearly states that sitagliptin should not be used in patients with type 1diabetes (Section 4.4).
History of ketoacidosis	The mechanism of action of sitagliptin precludes its being an effective antihyperglycemic agent in patients with type 1 diabetes mellitus. A history of ketoacidosis may suggest diagnosed or undiagnosed type 1 diabetes.	No	The sitagliptin EU SmPC clearly states that sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (Section 4.4).
Pregnancy or lactation	Due to limited data on the safety of use of sitagliptin during pregnancy, pregnant women were excluded from all clinical trials.	Yes	---
History of malignancy	In a clinical trial setting, recurring malignancy or treatment for malignancy may confound the assessment of safety and tolerability of sitagliptin.	No	Sitagliptin has no known deleterious effect, and does have altered efficacy, in patients with a history of malignancy
Patients with moderate and severe renal impairment was an exclusion in the majority of clinical trials, with the exception of Protocols 28, 63, 73, and 838 which investigated the safety and efficacy of sitagliptin in subjects with mild to severe renal impairment.	Renal function exclusion criteria varied across studies, based on renal exclusion criteria related to the use of metformin as background therapy, and on the need to adjust the dose of sitagliptin in subjects with moderate or severe renal insufficiency.	No	Sitagliptin has been studied in different trials both in patients with normal renal function and in patients with impaired renal function (up to ESRD). For patients with mild renal impairment (glomerular filtration rate [GFR] ≥60 mL/min to < 90 mL/min), no dosage adjustment for sitagliptin is required. A dose adjustment of sitagliptin is required for patients with moderate to severe renal impairment including ESRD. For patients with moderate renal impairment (GFR ≥ 45 mL/min. to <60 mL/min.), no dosage adjustment for sitagliptin is required. For patients with moderate renal impairment (GFR ≥30 mL/min to <45 mL/min), the dose of sitagliptin is 50 mg once daily. For patients with severe renal

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
			impairment (GFR ≥ 15 mL/min to <30 mL/min) or with end-stage renal disease (ESRD) (GFR < 15 mL/min), including those requiring hemodialysis or peritoneal dialysis, the dose of sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of dialysis.
ALT or AST >2.0-fold the ULN	In the setting of a clinical trial, impaired hepatic function may interfere with data interpretation.	No	This is typically a standard safety-related clinical trial exclusion criterion. Sitagliptin has no known deleterious effect and does not have altered efficacy in patients with a history of hepatic impairment.
Congestive Heart Failure was excluded in the majority of clinical trials.	In the setting of a clinical trial, a recent coronary event or intervention may interfere with data interpretation.	No	Sitagliptin has no known deleterious effect, and does not have altered efficacy in patients with congestive heart failure
For the majority of clinical trials, with the exception of TECOS: Within the past 3 or 6 months: Acute coronary syndrome (e.g. MI or unstable angina) Coronary artery intervention (e.g., CABG or PTCA) Stroke or transient ischemic neurologic disorder New or worsening signs or symptoms of heart disease.	In the setting of a clinical trial, a recent coronary event or intervention may interfere with data interpretation.	No	This is typically a standard safety-related clinical trial exclusion criterion. TECOS (trial P082 studied cardiovascular outcomes in patient with T2DM).
Use of recreational or illicit drugs or recent history of drug abuse or increased alcohol consumption	Acute alcohol intoxication and alcoholism may interfere with the adequate conduct of the clinical trial.	No	Sitagliptin has no known deleterious effects in acute alcohol intoxication.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme 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.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	There have been no clinical studies evaluating sitagliptin in pregnant women (including women with gestational diabetes) or lactating women. As of 25-OCT-2017, there were 31 reports of exposure during pregnancy in the sitagliptin and MK-0431A clinical development programs. These include 15 reports in women treated with sitagliptin (with or without metformin), 3 in women treated with either sitagliptin or placebo (codes unbroken), and 13 in women treated with placebo or an active comparator.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Hepatic, renal and cardiovascular impairment exposure can be found in Table SIII.2.6. Immunocompromised patients were not included in the pre-authorization clinical development program
Population with relevant different ethnic origin	See Table SIII.2.5and Table SIII.3.2 for race breakdown in clinical trials.
Subpopulations carrying relevant genetic polymorphisms	Not included in the pre-authorization clinical development program

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide unit distribution of sitagliptin/metformin FDC for the cumulative period from market introduction to 31-Dec-2019 is provided below. Estimates of patient exposure are also provided. This estimation was based upon a standard dosing regimen of two tablets daily, except for the 100 mg sitagliptin/1000 mg metformin XR tablet that is taken as a single tablet once daily. Patient exposure estimates were calculated from the Company's internal distribution data from the Worldwide Financial Repository System (WFRS) and the Financial Sharing Area databases. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide.

It is important to note that the estimated patient-years of treatment (PYT) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to sitagliptin/metformin FDC, since PYT estimates are calculated number of patients who could have been treated for one year based on the tablets distributed. However, since most patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher.

SV.1.2 Exposure

The estimated number of tablets of sitagliptin/metformin FDC Immediate Release (IR) distributed worldwide from product launch through 31-Dec-2019 is 22,798,602,444. This corresponds to 31,230,961 estimated patient years of treatment (PYT).

The estimated number of tablets of sitagliptin/metformin FDC Extended Release (XR) distributed worldwide from product launch through 31-Dec-2019 is 1,682,417,590. This corresponds to 2,949,680 estimated patient years of treatment (PYT).

Table SV.1.2.1: Post-marketing Exposure of Sitagliptin/Metformin FDC IR Cumulative to 31-Dec-2019

Strength	Distribution (total number of tablets)	Patient-Years of Treatment
IR 50/500 MG	4,514,241,505	6,183,892
IR 50/850 MG	2,829,288,228	3,875,737
IR 50/1000MG	15,455,072,711	21,171,332
Total	**22,798,602,444**	**31,230,961**

Table SV.1.2.2: Post-marketing Exposure of Sitagliptin/Metformin FDC XR Cumulative to 31-Dec-2019

Strength	Distribution (total number of tablets)	Patient-Years of Treatment
XR 50/500 MG	144,032,786	197,305
XR 50/1000 MG	1,067,536,020	1,462,378
XR 100/1000 MG	470,848,784	1,289,997
Total	**1,682,417,590**	**2,949,680**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Sitagliptin/metformin FDC is available only through prescribing physicians. Neither sitagliptin nor metformin is a drug with known psychotropic, mood-altering, or analgesic properties; therefore, it is highly unlikely that sitagliptin/metformin FDC would be sought out for illegal use.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

One important identified risk (lactic acidosis) and one important potential risk (pancreatic cancer) are discussed.

For the important identified risk, data from the 2011 Sitagliptin in Combination with Metformin Pooled Safety Population [Ref. 5.4: 03RTG9] is presented. For the important potential risk, data from the 2011 Sitagliptin Pooled Safety Population and the additional data from the results of P082 (TECOS) are included.

Table SVII.3.1.1: Details of Important Identified Risk: Lactic Acidosis

Frequency with 95% confidence interval (CI)	Lactic acidosis was observed in one subject in the co-administered sitagliptin/metformin treatment groups in the clinical studies. The reported incidence of lactic acidosis in patients receiving metformin is very low, approximately 0.03 cases/1000 patient-years [Ref. 5.4: 03Q0G7].

Person-time Adjusted Analysis of Subjects with Lactic Acidosis Adverse Events (Incidence > 0% in One or More Treatment Groups): 2011 Sitagliptin in Combination with Metformin Pooled Safety Population, Including Data After Initiation of Glycemic Rescue Therapy

Treatment	Number of Subjects With ≥ 1 Event / Subject-Years Follow-up Time (100-Subject-Years Incidence Rate)	Difference from Non-Exposed in Incidence Rate (95% CI)†
Subjects in Population		
Sitagliptin 100 mg	3624	
Non-Exposed	3388	
Selected Lactic Acidosis Adverse Events		
Sitagliptin 100 mg	1/3421 (0.0)	0.0
Non-Exposed	0/2974 (0.0)	
Investigations		
Sitagliptin 100 mg	1/3421 (0.0)	0.0
Non-Exposed	0/2974 (0.0)	
Blood lactic acid increased		
Sitagliptin 100 mg	1/3421 (0.0)	0.0
Non-Exposed	0/2974 (0.0)	

† Based on Miettinen & Nurminen method stratified by study and computed only for those endpoints with at least four patients having events in one or more treatment groups.

For subjects with ≥ 1 event, follow-up time is computed up to the time of the first event. For subjects without an event, follow-up time is computed up to the end of the treatment period + 14 days.

The details of the seriousness, outcome, and severity and nature of the risk of lactic acidosis are summarized below. The incidence tables are not provided due to the low incidences of the adverse experiences.

Seriousness / Outcomes	When it occurs, lactic acidosis is fatal in approximately 50% of cases [Ref. 5.4: 03R780]. No serious adverse events of lactic acidosis were reported in the 2011 Sitagliptin in Combination with Metformin Pooled Safety Population. One non-serious adverse event of blood lactic acid increased was reported and the outcome was unknown. However, one patient in the placebo group in P020 (add-on to metformin study) died of hepatic and renal failure on Study Day 602. This patient was hospitalized on Study Day 600 and, based on laboratory values, the patient was determined to have severe metabolic acidosis with increased lactic acid levels and acute renal failure. The autopsy report indicated that the possible cause of death was clinical hepatic failure.
Severity and Nature of the Risk	The one adverse event of blood lactic acid increased was moderate.
Risk Groups or Risk Factors	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Potential Mechanisms	Not defined.
Preventability	The risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin should be temporarily discontinued in patients undergoing radiologic procedures that involve iodinated contrast dyes.
Impact on the Risk-Benefit Balance of the Product	The important identified risk of lactic acidosis is a known rare effect that can occur due to metformin accumulation. This risk may be significantly decreased by regular monitoring of renal function and by temporarily discontinuing metformin in patients undergoing radiologic procedures that involve iodinated contrast dyes.
Potential Public Health Impact of Safety Concern	Very limited, since episodes of lactic acidosis related to metformin have been rare events.
Evidence Source	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Medical Dictionary For Regulatory Activities (MedDRA) Terms	Narrow Lactic acidosis Standardized MedDRA Queries (SMQ)

Table SVII.3.1.2: Details of Important Potential Risk: Pancreatic Cancer

Frequency with 95%CI	All Adverse Events 2011 Sitagliptin in Combination with Metformin Pooled Safety Population

Person-time Adjusted Analysis of Subjects with Pancreatic Cancer Adverse Events
(Incidence > 0% in One or More Treatment Groups):
2011 Sitagliptin in Combination with Metformin Pooled Safety Population,
Including Data After Initiation of Glycemic Rescue Therapy

Treatment	Number of Subjects With ≥ 1 Event / Subject-Years Follow-up Time (100-Subject-Years Incidence Rate)	Difference from Non-Exposed in Incidence Rate (95% CI)†
Subjects in Population		
Sitagliptin 100 mg	3624	
Non-Exposed	3388	
Selected Pancreatic Cancer Adverse Events		
Sitagliptin 100 mg	2/3421 (0.06)	0.02
Non-Exposed	1/2974 (0.03)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Sitagliptin 100 mg	2/3421 (0.06)	0.02
Non-Exposed	1/2974 (0.03)	
Adenocarcinoma pancreas		
Sitagliptin 100 mg	0/3421 (0.00)	-0.03
Non-Exposed	1/2974 (0.03)	
Pancreatic carcinoma		
Sitagliptin 100 mg	2/3421 (0.06)	0.05
Non-Exposed	0/2974 (0.00)	

† Based on Miettinen & Nurminen method stratified by study and computed only for those endpoints with at least four patients having events in one or more treatment groups.

For subjects with ≥ 1 event, follow-up time is computed up to the time of the first event. For subjects without an event, follow-up time is computed up to the end of the treatment period + 14 days.

Seriousness	Serious Adverse Events

Subjects With Pancreatic Cancer Serious Adverse Events by Seriousness Criterion (Incidence > 0% in One or More Treatment Groups): 2011 Sitagliptin in Combination with Metformin Pooled Safety Population, Including Data After Initiation of Glycemic Rescue Therapy

		Sitagliptin 100 mg		Non-Exposed	
	Seriousness Criterion	n	(%)	n	(%)
Subjects in population		3,624		3,388	
With one or more serious adverse events	Overall	2	(0.1)	1	(0.0)
	Cancer	2	(0.1)	1	(0.0)
	Congenital defect	0	(0.0)	0	(0.0)
	Death	0	(0.0)	0	(0.0)
	Disability	0	(0.0)	0	(0.0)
	Hospitalization	2	(0.1)	0	(0.0)
	Life threatening	1	(0.0)	0	(0.0)
	OME	0	(0.0)	0	(0.0)
	Overdose	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Adenocarcinoma pancreas	Overall	0	(0.0)	1	(0.0)
	Cancer	0	(0.0)	1	(0.0)
	Congenital defect	0	(0.0)	0	(0.0)
	Death	0	(0.0)	0	(0.0)
	Disability	0	(0.0)	0	(0.0)
	Hospitalization	0	(0.0)	0	(0.0)
	Life threatening	0	(0.0)	0	(0.0)
	OME	0	(0.0)	0	(0.0)
	Overdose	0	(0.0)	0	(0.0)
Pancreatic carcinoma	Overall	2	(0.1)	0	(0.0)
	Cancer	2	(0.1)	0	(0.0)
	Congenital defect	0	(0.0)	0	(0.0)
	Death	0	(0.0)	0	(0.0)
	Disability	0	(0.0)	0	(0.0)
	Hospitalization	2	(0.1)	0	(0.0)
	Life threatening	1	(0.0)	0	(0.0)
	OME	0	(0.0)	0	(0.0)

Subjects With Pancreatic Cancer Serious Adverse Events by Seriousness Criterion (Incidence > 0% in One or More Treatment Groups): 2011 Sitagliptin in Combination with Metformin Pooled Safety Population, Including Data After Initiation of Glycemic Rescue Therapy

		Sitagliptin 100 mg		Non-Exposed	
	Seriousness Criterion	n	(%)	n	(%)
Pancreatic carcinoma	Overdose	0	(0.0)	0	(0.0)

Every subject is counted once on each applicable row.
OME = other important medical event

Outcomes	All Adverse Events

Subjects With Pancreatic Cancer Adverse Events by Outcome (Incidence > 0% in One or More Treatment Groups): 2011 Sitagliptin in Combination with Metformin Pooled Safety Population, Including Data After Initiation of Glycemic Rescue Therapy

		Sitagliptin 100 mg		Non-Exposed	
	Outcome	n	(%)	n	(%)
Subjects in population		3,624		3,388	
With one or more adverse events	Overall	2	(0.1)	1	(0.0)
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(0.0)	1	(0.0)
	Resolved	1	(0.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Adenocarcinoma pancreas	Overall	0	(0.0)	1	(0.0)
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	0	(0.0)	1	(0.0)
	Resolved	0	(0.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
Pancreatic carcinoma	Overall	2	(0.1)	0	(0.0)
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(0.0)	0	(0.0)
	Resolved	1	(0.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)

Every subject is counted once on each applicable row.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Severity and Nature of the Risk	All Adverse Events

Subjects With Pancreatic Cancer Adverse Events by Maximum Intensity (Incidence > 0% in One or More Treatment Groups): 2011 Sitagliptin in Combination with Metformin Pooled Safety Population, Including Data After Initiation of Glycemic Rescue Therapy

	Intensity Grading	Sitagliptin 100 mg n	(%)	Non-Exposed n	(%)
Subjects in population		3,624		3,388	
With one or more adverse events	Total	2	(0.1)	1	(0.0)
	Mild	1	(0.0)	0	(0.0)
	Moderate	0	(0.0)	1	(0.0)
	Severe	1	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Adenocarcinoma pancreas	Total	0	(0.0)	1	(0.0)
	Moderate	0	(0.0)	1	(0.0)
Pancreatic carcinoma	Total	2	(0.1)	0	(0.0)
	Mild	1	(0.0)	0	(0.0)
	Severe	1	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event, and is classified according to the highest non-missing intensity grading.

Background Incidence / Prevalence	Incidence: United States (US): The incidence rate of pancreatic cancer in patients treated with sulfonylureas is 52.9 per 100,000 person-years. The incidence rate of pancreatic cancer in patients treated with metformin is 26.5 per 100,000 person-years. [Ref. 5.4: 04K85L] United Kingdom (UK): • 78.76 per 100,000 person-years (95% Cl: 71.54, 86.51) in patients with diabetes and 11.46 per 100, 000 person-years (95% Cl: 10.88, 12.06) in patients without diabetes at least 25 years old [Ref. 5.4: 03TBZ7]. • 70 per 100,000 person years among adults aged 18 years or older [Ref. 5.4: 03TBX7] • In a UK cohort study, patients with T2DM (0.3%) were 3 times more likely to develop pancreatic cancer than non-diabetic people (0.1%). [Ref. 5.4: 03RH5X]
Risk Groups or Risk Factors	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes. [Ref. 5.4: 03TBZ7]
Potential Mechanisms	There are no conclusive data to identify a mechanism by which DPP-4 inhibitors may cause pancreatic cancer.
Preventability	Data not available
Impact on the Risk-Benefit Balance	There is an increased risk of pancreatic cancer in patients with T2DM. In pre-clinical studies there are no indications for an increased carcinogenic risk associated with inhibition of DPP-4 enzyme activity. In clinical studies there was no significant difference between treatment groups in the incidence of pancreatic malignancies. Sitagliptin has positive impact on the long-term complications of diabetes, patient quality of life, and the prevention of the long-term microvascular complications of diabetes due to the important improvements in glycemic control.
Potential Public Health Impact of Safety Concern	The frequency of pancreatic cancer with sitagliptin and metformin is very low (see above), and this risk is expected to have minimal public health impact.
Evidence Source	In clinical studies (2011 Sitagliptin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
MedDRA Terms	Pancreatic neoplasms malignant (excl. islet cell and carcinoid) HLT

In P082, occurrence of confirmed charter-defined malignancies of the pancreas between the sitagliptin and placebo groups was analyzed as an endpoint of interest. Charter-defined pancreatic malignancy was classified as such if the patient had either evidence of a new pancreatic malignancy or the first recurrence (during the study period) of a previous pancreatic cancer.

There was no significant difference between treatment groups in the incidence of charter-defined pancreatic malignancies. However, in the ITT population, there were numerically fewer such events in the sitagliptin group than the placebo group.

In the analysis of the per-protocol (PP) population, 9/7257 patients in the sitagliptin group had a total of nine events of charter-defined pancreatic malignancy (0.1%; 0.05 per 100 person-years), and 10/7266 patients in the placebo group had a total of ten such events (0.1%; 0.05 per 100 person-years) (HR 0.91; 95% CI 0.37 to 2.25; p=0.846).

In the analysis of the ITT population, 9/7332 patients in the sitagliptin group had a total of nine events of charter-defined pancreatic malignancy (0.1%; 0.04 per 100 person-years); and 14/7339 patients in the placebo group had a total of 15 such events (0.2%; 0.07 per 100 person-years) (HR 0.66; 95% CI 0.28 to 1.51; p=0.322).

In the PP population, Kaplan-Meier curves and estimates for time to first charter-defined pancreatic malignancy showed no difference between the groups over time. In the ITT population, Kaplan-Meier curves and estimates for time to first charter-defined pancreatic malignancy in the two treatment groups started to diverge between month 12 and 18; thereafter, the percentage of patients with an event was numerically less over time in the sitagliptin group than in the placebo group through month 54.

Yearly through 3 years, only a small numerical difference was observed between treatment groups with regard to cumulative incidence of events of charter-defined pancreatic malignancy.

SVII.3.2 Presentation of the Missing Information

Missing information: Exposure during pregnancy and lactation

Evidence Source:

There are no adequate and well-controlled studies of sitagliptin/metformin FDC use during pregnancy or lactation

Population in Need of Further Characterisation:

There are not enough data from the use of sitagliptin/metformin FDC in pregnant women. Studies in animals have shown toxic effects on fetuses at high doses above those used in humans. Sitagliptin/metformin FDC is not recommended for use in pregnancy, as stated in the Product Information.

Sitagliptin was detected in breast milk when studies were performed in rats. No studies have been performed to find out whether sitagliptin is released into breast milk of nursing mothers who are taking this medicine. It is recommended that nursing mothers not take sitagliptin/metformin FDC while they are breast feeding.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Lactic acidosis
Important potential risks	• Pancreatic Cancer
Missing information	• Exposure during pregnancy and lactation

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, PSURs, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

The use of a specific adverse reaction follow-up questionnaire will be used for the adverse event of lactic acidosis.

Specific Adverse Reaction Follow-Up Questionnaires for Lactic acidosis:

A targeted questionnaire was implemented to request and obtain from the reporter all relevant follow-up information, including medical data available, regarding the condition lactic acidosis for each individual case safety report.

The following points were included in the questionnaire:

- Metabolic acidosis: lactate level, blood pH (arterial or venous), anion gap, ketonuria and β-hydroxybutyrate
- Metformin: daily dose; date/time/value of last dose, plasma level, concentration in erythrocytes
- Renal function: known values before and during the event
- Risk factors: alcohol use, exposure to contrast media, infection/sepsis, renal disease, dehydration, diarrhea, vomiting, acute heart failure, acute myocardial infarction, other conditions with hypoxia

III.2 Additional Pharmacovigilance Activities

Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

Table III.3.1: On-Going 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for sitagliptin/metformin FDC.

Table IV.1: Planned and On-Going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Lactic acidosis	Text in SmPC • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects No other routine risk minimization measures are proposed.
Pancreatic Cancer	No risk minimization proposed
Exposure during pregnancy and lactation	• SmPC: Section 4.6 Fertility, pregnancy, and lactation

V.2 Additional Risk Minimization Measures

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

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Lactic acidosis	SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects	Routine pharmacovigilance with use of a targeted questionnaire
Pancreatic Cancer	None	Routine Pharmacovigilance
Exposure during pregnancy and lactation	SmPC: Section 4.6 Fertility, pregnancy, and lactation	Routine Pharmacovigilance

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

I. Summary of Risk Management Plan for Janumet

This is a summary of the risk management plan (RMP) for Janumet. The RMP details important risks of Janumet, how these risks can be minimised, and how more information will be obtained about Janumet's risks and uncertainties (missing information).

Janumet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Janumet should be used.

This summary of the RMP for Janumet 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 Janumet's RMP.

I.A The Medicine and What It Is Used For

Janumet is authorised for treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Janumet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Janumet is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Janumet is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Refer to SmPC for the full indication.

It contains sitagliptin phosphate and metformin hydrochloride as the active substances and it is given by oral route of administration.

Further information about the evaluation of Janumet's benefits can be found in Janumet's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000861/human_med_000864.jsp&mid=WC0b01ac058001d124

I.B Risks Associated With The Medicine and Activities to Minimise or Further Characterise The Risks

Important risks of Janumet, together with measures to minimise such risks and the proposed studies for learning more about Janumet's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* 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 Janumet is not yet available, it is listed under 'missing information' below.

I.B.1 List of Important Risks and Missing Information

Important risks of Janumet are risks that need special risk management activities to further investigate or minimise 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 Janumet. 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 I.B.1.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

Janumet has been marketed for 11 years since 2007 with over 25 million patient-years of treatment. The safety profile has been well-characterised during that time and adverse reactions that have been reported from clinical trials, non-interventional studies and post-approval safety surveillance analysis are included in the SmPC. There are no studies planned or warranted to further characterise any identified or potential risk that would alter the established risk-benefit profile for Janumet. There are no additional important safety concerns for which prospective additional risk management is to be planned.

In conclusion, continued spontaneous safety surveillance and use of a lactic acidosis questionnaire as part of the routine pharmacovigilance activities will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimisation.

I.B.2 Summary of Important Risks

Table I.B.2.1: Important Identified Risk: Lactic Acidosis

Evidence for linking the risk to the medicine	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Risk factors and risk groups	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Risk minimisation measures	Routine risk minimisation measuresSmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects

Table I.B.2.2: Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	In clinical studies (2011 Sitagliptin in Combination with Metformin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
Risk factors and risk groups	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes. [Ref. 5.4: 03TBZ7]
Risk minimisation measures	None; Routine pharmacovigilance only

Table I.B.2.3: Missing Information: Exposure During Pregnancy and Lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Fertility, pregnancy, and lactation

I.B.3 Post-Authorisation Development Plan

I.B.3.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Janumet.

I.B.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Janumet.

II. Summary of Risk Management Plan for Velmetia

This is a summary of the risk management plan (RMP) for Velmetia. The RMP details important risks of Velmetia, how these risks can be minimised, and how more information will be obtained about Velmetia's risks and uncertainties (missing information).

Velmetia's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Velmetia should be used.

This summary of the RMP for Velmetia 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 Velmetia's RMP.

II.A The Medicine and What It Is Used For

Velmetia is authorised for treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Velmetia is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Velmetia is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Velmetia is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Refer to SmPC for the full indication.

It contains sitagliptin phosphate and metformin hydrochloride as the active substances and it is given by oral route of administration.

Further information about the evaluation of Velmetia's benefits can be found in Velmetia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000862/human_med_001131.jsp&mid=WC0b01ac058001d124

II.B Risks Associated with The Medicine and Activities to Minimise or Further Characterise The Risks

Important risks of Velmetia, together with measures to minimise such risks and the proposed studies for learning more about Velmetia's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* 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 Velmetia is not yet available, it is listed under 'missing information' below.

II.B.1 List of Important Risks and Missing Information

Important risks of Velmetia are risks that need special risk management activities to further investigate or minimise 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 Velmetia. 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 II.B.1.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

Velmetia has been marketed for 11 years since 2007 with over 25 million patient-years of treatment. The safety profile has been well-characterised during that time and adverse reactions that have been reported from clinical trials, non-interventional studies and post-approval safety surveillance analysis are included in the SmPC. There are no studies planned or warranted to further characterise any identified or potential risk that would alter the established risk-benefit profile for Velmetia. There are no additional important safety concerns for which prospective additional risk management is to be planned.

In conclusion, continued spontaneous safety surveillance and use of a lactic acidosis questionnaire as part of the routine pharmacovigilance activities will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimisation.

II.B.2 Summary of Important Risks

Table II.B.2.1: Important Identified Risk: Lactic Acidosis

Evidence for linking the risk to the medicine	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Risk factors and risk groups	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Risk minimisation measures	Routine risk minimization measures SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects

Table II.B.2.2: Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	In clinical studies (2011 Sitagliptin in Combination with Metformin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
Risk factors and risk groups	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes. [Ref. 5.4: 03TBZ7]
Risk minimisation measures	None; Routine pharmacovigilance only

Table II.B.2.3: Missing Information: Exposure During Pregnancy and Lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Fertility, pregnancy, and lactation

II.B.3 Post-Authorisation Development Plan

II.B.3.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Velmetia.

II.B.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Velmetia.

III. Summary of Risk Management Plan for Efficib

This is a summary of the risk management plan (RMP) for Efficib. The RMP details important risks of Efficib, how these risks can be minimised, and how more information will be obtained about Efficib's risks and uncertainties (missing information).

Efficib's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Efficib should be used.

This summary of the RMP for Efficib 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 Efficib's RMP.

III.A The Medicine and What It Is Used For

Efficib is authorised for treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Efficib is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Efficib is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise

in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Efficib is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Refer to SmPC for the full indication.

It contains sitagliptin phosphate and metformin hydrochloride as the active substances and it is given by oral route of administration.

Further information about the evaluation of Efficib's benefits can be found in Efficib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000896/human_med_000755.jsp&mid=WC0b01ac058001d124

III.B Risks Associated with The Medicine and Activities to Minimise or Further Characterise The Risks

Important risks of Efficib, together with measures to minimise such risks and the proposed studies for learning more about Efficib's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* 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 Efficib is not yet available, it is listed under 'missing information' below.

III.B.1 List of Important Risks and Missing Information

Important risks of Efficib are risks that need special risk management activities to further investigate or minimise 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 Efficib. 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 III.B.1.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

Efficib has been marketed for 11 years since 2007 with over 25 million patient-years of treatment. The safety profile has been well-characterised during that time and adverse reactions that have been reported from clinical trials, non-interventional studies and post-approval safety surveillance analysis are included in the SmPC. There are no studies planned or warranted to further characterise any identified or potential risk that would alter the established risk-benefit profile for Efficib. There are no additional important safety concerns for which prospective additional risk management is to be planned.

In conclusion, continued spontaneous safety surveillance and use of a lactic acidosis questionnaire as part of the routine pharmacovigilance activities will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimisation.

III.B.2 Summary of Important Risks

Table III.B.2.1: Important Identified Risk: Lactic Acidosis

Evidence for linking the risk to the medicine	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Risk factors and risk groups	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Risk minimisation measures	Routine risk minimization measures SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects

Table III.B.2.2: Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	In clinical studies (2011 Sitagliptin in Combination with Metformin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
Risk factors and risk groups	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes. [Ref. 5.4: 03TBZ7]
Risk minimisation measures	None; Routine pharmacovigilance only

Table III.B.2.3: Missing Information: Exposure During Pregnancy and Lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Fertility, pregnancy, and lactation

III.B.3 Post-Authorisation Development Plan

III.B.3.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Efficib.

III.B.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Efficib.

IV. Summary of Risk Management Plan For Ristfor

This is a summary of the risk management plan (RMP) for Ristfor. The RMP details important risks of Ristfor, how these risks can be minimised, and how more information will be obtained about Ristfor's risks and uncertainties (missing information).

Ristfor's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ristfor should be used.

This summary of the RMP for Ristfor 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 Ristfor's RMP.

IV.A The Medicine and What It Is Used For

Ristfor is authorised for treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Ristfor is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Ristfor is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Ristfor is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Refer to SmPC for the full indication.

It contains sitagliptin phosphate and metformin hydrochloride as the active substances and it is given by oral route of administration.

Further information about the evaluation of Ristfor's benefits can be found in Ristfor's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001235/human_med_001330.jsp&mid=WC0b01ac058001d124

IV.B Risks Associated with The Medicine and Activities to Minimise or Further Characterise The Risks

Important risks of Ristfor, together with measures to minimise such risks and the proposed studies for learning more about Ristfor's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* 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 Ristfor is not yet available, it is listed under 'missing information' below.

IV.B.1 List of Important Risks and Missing Information

Important risks of Ristfor are risks that need special risk management activities to further investigate or minimise 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 Ristfor. 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 IV.B.1.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

Ristfor has been marketed for 11 years since 2007 with over 25 million patient-years of treatment. The safety profile has been well-characterised during that time and adverse reactions that have been reported from clinical trials, non-interventional studies and post-approval safety surveillance analysis are included in the SmPC. There are no studies planned or warranted to further characterise any identified or potential risk that would alter the

established risk-benefit profile for Ristfor. There are no additional important safety concerns for which prospective additional risk management is to be planned.

In conclusion, continued spontaneous safety surveillance and use of a lactic acidosis questionnaire as part of the routine pharmacovigilance activities will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimisation.

IV.B.2 Summary of Important Risks

Table IV.B.2.1: Important Identified Risk: Lactic Acidosis

Evidence for linking the risk to the medicine	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Risk factors and risk groups	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Risk minimisation measures	Routine pharmacovigilance with use of a targeted questionnaire SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects

Table IV.B.2.2: Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	In clinical studies (2011 Sitagliptin in Combination with Metformin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
Risk factors and risk groups	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes. [Ref. 5.4: 03TBZ7]
Risk minimisation measures	None; Routine pharmacovigilance only

Table IV.B.2.3: Missing Information: Exposure during pregnancy and lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Fertility, pregnancy, and lactation

IV.B.3 Post-Authorisation Development Plan

IV.B.3.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ristfor.

IV.B.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Ristfor.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Lactic acidosis questionnaire attached

MSD

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

The name of entity "Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. "or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an MSD product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INTITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, MSD subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that MSD respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. For instructions on how to return this form, please contact your local MSD representative or office.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about our company's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance

MERCK

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an Merck product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INTITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 600-705-1685, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-661-6229.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privecy/

Sincerely,

Global Pharmacovigilance
Phone: 1-800-705-1685
Fax: 215-661-6229

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

DRUG ADVERSE EXPERIENCE REPORT

Program ID Number:

Today's date:
Please use this format throughout form ➔ DD/MM/YY

1. Reporter Information		2. Patient Information		
Name:		Name or intitials:		Date of birth:
Title:		Zip code:	Age:	☐ Male ☐ Female
Institution:		Occupation:	Height: ☐IN ☐CM	Weight: ☐LB ☐KG
Address:		Is the patient pregnant? ☐ No ☐Yes	Weeks gestation: Date of LMP:	Gravida: Para:
Telephone #:	Fax #:	Race/ethnicity: ☐Caucasian ☐Black ☐Asian ☐Hispanic ☐Native American ☐Multiracial ☐Other:		

3. Merck Product Information

Merck Product Name	Suspect Therapy	Dose/ Route	Frequency	Indication	Start Date	Stop Date	LOT Number/ Expiration Date	Was product interrupted or discontinued?	Re-start date if applicable
	☐No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	

4. Patient's experience(s) (list most significant first)	Onset date/ Duration	Did experience abate after stopping drug?	Did experience reappear after reintroduction?	Event Criteria	Outcome
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving

**** Important Medical Event (IME): Required Medical/Surgical Intervention to prevent one of the event criteria listed.**

5. Only complete this section if there was a medication error. (Medication error: an unintended failure in the drug treatment process that led to, or had the potential to lead to an adverse event):

Indicate at which point in the process the medication error occurred:
☐Prescribing ☐Storage in clinical Practice ☐Dispensing ☐Preparation for Administration ☐Administration
Please describe the error, any contributing factors that led to the error, and any corrective actions taken (if applicable) in the fields and narrative description.

6. Did the patient die?	7. Was autopsy performed?	8. Was prescription drug treatment for the experience required?
☐No ☐Yes List date narrative	☐No ☐Yes If available, please provide copy of death certificate and/or autopsy results.	☐No ☐Yes List in narrative section, with start and stop date (or ongoing).

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

9. Please list all concomitant medications:

Product Name	Suspect Therapy	Route	Dose	Total Daily Dosage	Start Date	Stop Date	Indication
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						

10. Concurrent Conditions:
(Medical conditions that developed prior to the initiation of drug therapy and were unresolved at the time of the first adverse event)

11. Past Medical History:
(Events preceding the occurrence of the adverse event – list any pertinent information, including past drug reaction or allergies, start and stop dates)

12. Provide a Narrative Description of the events including labs/diagnostic tests to support AE information or attach results:

(Please attach additional pages as necessary)

Medical/Surgical intervention to prevent one of the event criteria listed? ☐No ☐Yes
If yes, please be sure to include above in EVENT CRITERIA as IME

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

TARGETED QUESTIONNAIRE – LACTIC ACIDOSIS

DID THE PATIENT EXPERIENCE LACTIC ACIDOSIS? ☐ **No** ☐ **Yes**

→ If yes, please complete this form and return with any supporting documentation to Pharmacovigilance *(refer to Instructions on Page 1)*.

REPORTER INFORMATION

Name and title:

Affiliation:

Address:

Daytime Telephone Number:

Signature and date:

PATIENT INFORMATION

Patient initials: ☐ **Male** ☐ **Female** **Age or DOB** (DD/MM/YY):

PRODUCT INFORMATION

Suspect Product: *Lot # & Exp. Date* (DD/MM/YY):	**Dose:**	**Route:**	**Frequency:**	**Start Date** (DD/MM/YY):	**Date/Time of last dose before event** (DD/MM/YY):	**Ongoing?** ☐ **Yes** ☐ **No** *If no, please provide stop date* ►	**Stop Date** (DD/MM/YY):

Was drug discontinued due to lactic acidosis event? ☐ **Yes** → If yes, did the event resolve after the drug was discontinued? ☐ **Yes** ☐ **No**
☐ **No**

Was drug dose changed due to lactic acidosis event? ☐ **Yes** → If yes, specify new dose: _____
☐ **No** If yes, did the event resolve after the drug was changed? ☐ **Yes** ☐ **No**

If drug was discontinued due to lactic acidosis, was the drug re-introduced? ☐ **Yes** ☐ **No**
If yes, did the event reoccur or worsen after re-introduction? ☐ **Yes** ☐ **No**

Was the patient taking other metformin-containing drug(s) together with the suspect product? ☐ Yes ☐ No
If yes, please provide the dosing details for the other metformin-containing drug(s) below.

Name(s) of metformin-containing product(s):	**Dose:**	**Route:**	**Frequency:**	**Start Date** (DD/MM/YY):	**Date/Time of last dose before event** (DD/MM/YY):	**Ongoing?** ☐ **Yes** ☐ **No** *If no, please provide stop date* ►	**Stop Date** (DD/MM/YY):

Was drug discontinued due to lactic acidosis event? ☐ **Yes** → If yes, did the event resolve after the drug was discontinued? ☐ **Yes** ☐ **No**
☐ **No**

Was drug dose changed due to lactic acidosis event? ☐ **Yes** → If yes, specify new dose: _____
☐ **No** If yes, did the event resolve after the drug was changed? ☐ **Yes** ☐ **No**

If drug was discontinued due to lactic acidosis, was the drug re-introduced? ☐ **Yes** ☐ **No**
If yes, did the event reoccur or worsen after re-introduction? ☐ **Yes** ☐ **No**

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

LACTIC ACIDOSIS ADVERSE EVENT INFORMATION

Onset of Event: (Initial onset of symptoms)

Date (DD/MM/YY):

Time:

Did the event of lactic acidosis require the patient to be admitted to the hospital? ☐ No ☐ Yes
Dates of hospitalization (DD/MM/YY): _____ to _____
Did the event of lactic acidosis cause the patient's pre-existing hospitalization to be prolonged?
☐ No ☐ Yes, date it became prolonged: _____
Do any of the following serious criteria apply to the event of lactic acidosis (check all that applies)**?**
☐ Resulted in death ☐ Was life-threatening ☐ Resulted in disability/incapacity ☐ Was a congenital anomaly/birth defect

Description of Lactic Acidosis Event - Please provide complete details of the event including presenting symptoms and signs, chronology and clinical evolution (use additional pages if necessary):

***Please attach any supporting documentation (e.g., diagnostic test results, discharge summaries).*

Event outcome:

☐ **Complete Recovery** Date of resolution (DD/MM/YY): _____
☐ **Recovered with residual effects** Date of resolution (DD/MM/YY): _____ Residual effects: _____
☐ **Continuing**
☐ **Fetal** Date of death _____ Autopsy done: ☐No ☐Yes (If yes, please attach autopsy report.) Cause of death:_____
☐ **Unknown**

Did the patient have any of the following pre-existing or concurrent conditions at the time of or during the period leading up to the lactic acidosis event? Check all that apply and note date of onset next to the condition:

☐ Renal impairment, *specify:*
☐ Infection or sepsis syndrome, *specify:*
☐ Acute heart failure
☐ Acute *myocardial* infarction
☐ Cardiac arrest or sustained hypotension
☐ Other conditions with hypoxia, *specify:*
☐ Status epilepticus
☐ Sustained muscle twitching or rigidity
☐ Hepatic impairment (e.g. cirrhosis, hepatitis), *specify:*
☐ Metabolic acidosis
☐ Cancer, *specify:*
☐ HIV or AIDS
☐ Alcohol use, *specify:*
☐ Exposure to contrast media, *specify:*
☐ Vomiting
☐ Diarrhea
☐ Dehydration
☐ Hypovolemia
☐ Recent trauma or surgery, *specify:*
☐ Tissue necrosis, *specify:*
☐ Prolonged exercise
☐ Drug abuse
☐ Exposure to noxious substances, *specify:*
☐ Malnutrition
☐ Other, *specify:*

Please provide any other information of relevance in including medical history/ environmental exposure/ occupation:

Which symptoms or findings were reported or observed? Check all that apply and note date of onset next to the symptom:

☐ Vomiting
☐ Abdominal pain
☐ Mus
☐ Dyspnea
☐ Asthenia
☐ Hypothermia
☐ Other – please specify:

LACTIC ACIDOSIS QUESTIONNAIRE

MARRS#: [INSERT MARRS NUMBER]

Please provide any diagnostic testing results drawn at the time points below:						
Diagnostic Tests	Normal range (with units)	Baseline level (prior to first dose of drug)	During treatment but before onset of symptoms	Onset of symptoms	Resolution of symptoms	Other: _____
DATE (MM/DD/YY) ►►						
Lactate						
Blood pH (arterial)						
Blood pH (venous)						
Anion gap						
Bicarbonate						
Ketone (blood)						
Ketone (urine)						
β-hydroxybutyrate						
Metformin (plasma)						
Metformin (erythrocytes)						
BUN						
Creatinine						
Creatinine clearence						
eGFR						

☐ **Laboratory results attached** ☐ **Additional page(a) attached**

What treatment(s) was/were administered for the event?

Was hemodialysis performed? If so, please provide details including metformin levels.

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.