Risk Management Plan

Active substances (INN or common name):	**Metformin hydrochloride** **Metformin embonate**
Name of Company:	**Merck Healthcare KGaA** **Frankfurter Straße 250** **D-64293 Darmstadt** **Telephone +49 61 51-72 0** **Telefax +49 61 51-72 69 14** **E-Mail:** PPD

RMP version to be assessed as part of this application:

RMP version number:	8.1
Data lock point for this RMP:	01 October 2020
Date of final sign off:	Document signed electronically, see date of eSignature at the end of the document
Rationale for submitting an updated RMP:	Health Authority comments received during the variation procedure FR/H/xxx/WS/233
Summary of significant changes in this RMP:	Update of the Missing information: Long-term offspring outcomes after exposure to metformin in utero • Rationale provided why 'lactation' has been removed • Incidence of hyperglycemia in pregnancy and periconceptional phase provided • Information on treatment of hyperglycemia during pregnancy provided • Results from additional analysis of PASS CLUE added RMP harmonized with Guidance on the format of RMP in the EU

Details of the currently approved RMP:

Version number:	7.2
Approved with procedure:	FR/H/xxxx/WS/0153
Date of approval (opinion date):	10 March 2020

Signatures

Name:	PPD
	Qualified Person responsible for Pharmacovigilance in the European Economic Area (EEA QPPV)
	QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder´s QPPV.
	The electronic signature is available on file.
Signature:	Document signed electronically

Name:	PPD
	Global Patient Safety, Safety Strategy Lead
	(contact person for this RMP)
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Signature:	Document signed electronically

Name:	PPD
	Global Patient Safety, Senior Medical Director
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List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	Angiotensin Converting Enzyme
AD	Alzheimer Disease
ADA	American Diabetes Association
AE	Adverse Event
ANCA	Antineutrophil Cytoplasmic Antibody
ATP	Adenosine-Tri-Phosphate
AUC	Area Under the Curve
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CIN	Contrast Induced Nephropathy
CKD	Chronic Kidney Disease
Cmax	Maximal Concentration
COX	Cyclooxygenase
CPRD	Clinical Practice Research Datalink
CrCl	Creatinine Clearance
CVD	Cardiovascular Disease
DDD	Defined Daily Dose
DKD	Diabetic Kidney Disease
Dl	Decilitre
DLP	Data Lock Point
DM	Diabetes Mellitus
DPP	Diabetes Prevention Program
DPP-4 inhibitor	Dipeptidyl peptidase-4 inhibitor
DPPOS	Diabetes Prevention Program Outcome Study
EASD	European Association for the study of Diabetes
EEA	European Economic Area
EMA	European Medicines Agency

EPIC	European Prospective Investigation into Nutrition and Cancer
ERA-EDTA	European Renal Association / European Dialysis and Transplant Association
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FPI	First Patient In
GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
GIR	Glucophage immediate release
GLP	Glucagon-like Peptide
GPS	Global Patient Safety
GXR	Glucophage extended release
HbA1c	Haemoglobin A1c
H2-antagonist	Histamine 2 antagonist
HCl	Hydrochloride
holoTCII	Holotranscobalamin
HR	Hazard Ratio
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IR	Immediate Release
L	Litre
LA	Lactic Acidosis
LPI	Last Patient In
MAH	Marketing Authorization Holder
MALA	Metformin-associated Lactic Acidosis
MATE	Multidrug and Toxin Extrusion protein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Ml	Millilitre
MI	Myocardial Infarction
MiG	Metformin in Gestational Diabetes
Min	Minute
MMA	Methylmalonic acid
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NGT	Normal Glucose Tolerance
NKF	National Kidney Foundation
NMDA	N-methyl-D-aspartate
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Oral Contraceptives
OCP	Oral Contraceptive Product
OCT	Organic Cation Transporter
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PCOS	Polycystic Ovarian Syndrome
PIL	Patient Information Leaflet
PPI	Proton Pump Inhibitor
PT	Preferred Term
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PBRER	Periodic Benefit Risk Evaluation Report
PVAR	Preliminary Variation Assessment Report
RCT	Randomized Clinical Trial
RMS	Reference Member State
RR	Relative Risk

SGLT-2	Sodium Glucose Cotransporter 2
SmPC	Summary of Product Characteristics
SMQ	Standard Medical Query
T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USA	United States of America
WHO	World Health Organization
XR	Extended Release

Part I: Product Overview

Product Overview

Active substances (INN or common name)	Metformin hydrochloride Metformin embonate
Pharmacotherapeutic group (ATC Code)	A10BA02
Marketing Authorization Holder	MAH in the Reference Member State of the Mutual Recognition Procedure (France): Merck Santé s.a.s. 37 rue Saint-Romain 69008 Lyon (France) All MAs concerned are considered to belong to the 'same marketing authorization holder', as per the Commission communication 98/C 229/03
Medicinal products to which this RMP refers	Glucophage® film-coated tablets (metformin hydrochloride immediate release formulation; IR) Glucophage® prolonged release tablets (metformin hydrochloride prolonged release formulation; XR) Stagid® (metformin embonate immediate release formulation)
Invented names in the European Economic Area (EEA)	Glucophage® (metformin hydrochloride) and associated names Stagid® (metformin embonate)
Marketing authorization procedure	Glucophage® IR: Mutual Recognition Procedure, National Procedure Glucophage® XR: National Procedure Stagid®: National Procedure
Brief description of the product	<u>Chemical class</u> Metformin as biguanide (N,N-dimethylimidodicarbonimidic diamide; 1,1-dimethylbiguanide) is not chemically or pharmacologically related to any other class of approved oral anti-hyperglycemic agents.
	<u>Summary of mode of action</u> Metformin improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose.

	Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycemic agents. Metformin decreases hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, decreases intestinal absorption of glucose, and increases insulin sensitivity by improving peripheral glucose uptake and utilization. Metformin, when used alone, does not produce hypoglycemia in patients with type 2 diabetes mellitus and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting, insulin levels and daylong plasma insulin response may actually decrease.
	Important information about its composition Metformin is available in two different salts: Metformin hydrochloride and metformin embonate. Metformin hydrochloride exists in two pharmaceutical formulations by Merck, immediate release (IR) film coated tablets and prolonged release (XR) tablets. Each film-coated (IR) tablet contains 500 mg, 850 mg or 1000 mg metformin hydrochloride corresponding to 390 mg, 663 mg or 780 mg metformin base, respectively. Each prolonged-release (XR) tablet contains 500 mg, 750 mg, 850 mg or 1000 mg metformin hydrochloride corresponding to 390 mg, 585 mg, 663 mg or 780 mg metformin base, respectively. Metformin hydrochloride XR consists of the API embedded in a dual hydrophilic polymer matrix system. Metformin hydrochloride is released slowly from the XR dosage form via diffusion through the gel matrix that is essentially independent of pH. Metformin embonate is available as a single dose immediate release tablet, containing 700 mg metformin embonate, which corresponds to 280 mg of metformin base.
Hyperlink to the Product Information	Not applicable

Indications in the EEA	**Metformin hydrochloride IR:** Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycemic control. • In adults, metformin may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin. • In children from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin. A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure. **Metformin hydrochloride XR:** As above with the exception of children and adolescents **Metformin hydrochloride IR and XR:** applies only if prediabetes indication extension is approved {Tradename IR and XR}: Prevention of type 2 diabetes mellitus in patients with prediabetes and at least one additional risk factor in whom life style modifications alone have not reached adequate glycemic control (please refer to Annex 7b for countries this indication is approved in). **Metformin embonate** Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. In adults, metformin embonate may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin. Treatment of type 1 diabetes (insulin-dependent diabetes) in adult patients, in combination with insulin therapy
	<u>Proposed</u> Not applicable

<table>
<tr><td>Dosage in the EEA</td><td>Maximum daily dose in adults:
Metformin hydrochloride IR: 3000 mg corresponding to 2340mg base
Metformin hydrochloride XR: 2000 mg corresponding to 1560mg base
Metformin embonate: 8 tablets corresponding to 2240 mg base
Maximum daily dose in children
Metformin hydrochloride IR: 2000 mg corresponding to 1560mg base
Maximum daily dose in patients with renal impairment
<table>
<tr><th>GFR ml/min</th><th>Total maximum daily dose</th></tr>
<tr><td>60-89</td><td>Metformin hydrochloride IR: 3000 mg
Metformin hydrochloride XR: 2000 mg
Metformin embonate: 8 tablets</td></tr>
<tr><td>45-59</td><td>Metformin hydrochloride IR and XR: 2000 mg
Metformin embonate: 6 tablets</td></tr>
<tr><td>30-44</td><td>Metformin hydrochloride IR and XR: 1000 mg
Metformin embonate: 3 tablets</td></tr>
<tr><td><30</td><td>Metformin is contraindicated</td></tr>
</table>
<u>All formulations and salts</u>:
Dose, frequency, and duration of administration should be according to respective Summary of Product Characteristics (SmPC).</td></tr>
<tr><td></td><td><u>Proposed</u> (if applicable):
None</td></tr>
<tr><td>Pharmaceutical forms and strengths</td><td><u>Current:</u>
Glucophage®, film-coated tablets (IR) (500 mg, 850 mg and 1000 mg metformin hydrochloride)
Glucophage®, prolonged release (XR) tablets (500 mg, 750 mg, and 1000 mg metformin hydrochloride)
Stagid® tablet (700 mg metformin embonate)</td></tr>
<tr><td></td><td><u>Proposed</u>:
Addition of:
Glucophage®, prolonged release (XR) tablets (850 mg metformin hydrochloride)</td></tr>
</table>

Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI Epidemiology of the Indications and Target Populations

Type 2 Diabetes

Diabetes mellitus describes a metabolic disorder categorized by chronic hyperglycemia resulting from insufficient insulin secretion, insulin resistance or both. This in turn leads to disturbances of the carbohydrate, fat, and protein metabolism. Diabetes mellitus is therefore often associated with hypertension, dyslipidemia and central obesity, and is part of the metabolic syndrome (ADA, 2017). The disease has a long asymptomatic phase, but complications are usually present at the time of diagnosis (IDF, 2015).

Type 2 diabetes mellitus (T2DM) is usually acquired secondarily and during adulthood, with a tendency to earlier onset, especially relating to obesity, even in adolescence and childhood (Copeland, 2013). It accounts for 90-95% of patients with diabetes (ADA, 2017).

The diagnosis of T2DM is, as per WHO criteria, based on a HbA1c ≥6.5%; or fasting plasma glucose (FPG) ≥126mg/dl (7.0mmol/l); or 2-hour plasma glucose ≥200mg/dl (11.1mmol/l) in a 75g oral glucose tolerance testing (OGTT); or a random plasma glucose ≥200mg/dl (11.1mmol/l) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis (ADA, 2017; IDF 2013; Colagiuri, 2011).

Incidence and prevalence

T2DM is a world-wide health concern, with the global prevalence estimated to be as high as 9% amongst adults aged 18+ years, and the WHO predicting it to be the 7th leading cause of death in 2030 (WHO, 2016). It is estimated that up to half of cases of type 2 diabetes in the general population may be undiagnosed (Forouhi, 2014, IDF, 2015). In children < 17 years, an incidence of 0.72/100 000 (95% CI 0.58–0.88) children was found (Candler, 2018).

Risk factors

The rapid rise in the number of people with type 2 diabetes worldwide is associated with an ageing population, economic development, increasing urbanisation, less healthy diets and reduced physical activity (IDF, 2015). Prediabetes, which is an indication of metformin hydrochloride, is also a risk factor for type 2 diabetes, increasing the risk by 3- to 10-fold (Yang, 2015). Several risk factors play a part in the development of type 2 diabetes, particularly excess bodyweight, increasing age, poor diet and physical inactivity (Tamayo, 2014; IDF, 2015).

Type 2 diabetes has a strong genetic component. Genome-wide association studies have identified >60 genetic variants associated with type 2 diabetes, but individual effects of genetic variants are

considered small (Tamayo, 2014). Gestational diabetes is associated with an increased risk of both mother and child developing type 2 diabetes later in life. It is estimated that one in seven births is affected by gestational diabetes (IDF, 2015). In-utero exposure to maternal smoking may also predispose to diabetes and other metabolic disturbances in the offspring (Tamayo, 2014).

Emerging evidence suggests that exposure to environmental pollutants (e.g. nitrogen oxides, fine particulate matter, man-made persistent organic pollutants), psychosocial factors (e.g. emotional stress, anxiety, depressive disorders) and biomarkers of metabolic pathways (e.g. markers of subclinical inflammation, oxidative stress, endothelial and renal dysfunction) may contribute to developing type 2 diabetes (Tamayo, 2014).

Mortality

Life expectancy was found to be shortened by 6–8 years in UK patients presenting with type 2 diabetes at age 50, compared to the general population (Nwaneri, 2012). The most common cause of death among patients with type 2 diabetes is myocardial infarction (MI) (Holman, 2008; Seshasai, 2011). Although the risk of MI may be reduced by good control of cholesterol, blood pressure and blood glucose, an excess risk of death still exists in those with type 2 diabetes (Lind, 2013; IDF, 2015).

A Swedish registry-based study looked at the risk of death from any cause and from cardiovascular causes in more than 400,000 type 2 diabetes patients, according to glycemic control and renal complications (Tancredi, 2015). Overall, 17.7% of 435,369 patients with diabetes died, compared with 14.5% of 2,117,483 controls (adjusted HR, 1.15; 95% CI: 1.14–1.16). The rate of cardiovascular death was 7.9% among patients versus 6.1% among controls (adjusted HR 1.14; 95% CI: 1.13–1.15).

In terms of glycemic control, those patients with type 2 diabetes and a time-updated mean HbA1c of 6.9% or less and aged less than 55 years, the excess risks of death were approximately twice as high as the risks among controls (HR for death from any cause, 1.92; 95% CI: 1.75–2.11; HR for cardiovascular death, 2.18; 95% CI: 1.81–2.64). In the same group, patients 75 years of age or older had lower risks of death than controls (HR for death from any cause, 0.95; 95% CI: 0.94–0.96; HR for cardiovascular death, 0.92; 95% CI: 0.90–0.94) (Tancredi, 2015).

In patients in the highest category of glycated hemoglobin level HbA1c ≥9.7%), for those younger than 55 years of age, the HR for death from any cause, as compared with controls, was 4.23 (95% CI: 3.56–5.02) and the HR for cardiovascular death was 5.38 (95% CI: 3.89–7.43). In patients 75 years of age or older in the same group, the corresponding HR for death from any cause was 1.55 (95% CI: 1.47–1.63) and the HR for cardiovascular death was 1.42 (95% CI: 1.32–1.53) (Tancredi, 2015).

A decline in diabetes-related mortality has been observed in recent years in Europe and other regions such as the USA. Cardiovascular disease (CVD)-related mortality in type 2 diabetes patients was compared between two cohorts, ten years apart. CVD-mortality had declined by 32% and all-cause mortality by 19% (Olafsdottir, 2013). Mortality rates were also found to have dropped from 117 to 46 per 1000 persons during the eight-year follow-up of a British study (Gulliford, 2009; Olafsdottir, 2013). An increased mortality appears however to be prevalent already in undiagnosed diabetes (Tamayo, 2014).

Prediabetes

Type 2 diabetes is characterized by insulin resistance, in which the action of insulin on glucose metabolism is blunted (DeFronzo, 1992; DeFronzo, 1997). Increased secretion of insulin masks the presence of insulin resistance early during diabetes; however, a progressive loss of β-cell mass and β-cell function leads to a relative deficit of insulin release, at which point loss of normal glucose regulation occurs (Nathan, 2007).

Prediabetes initially presents as impaired glucose tolerance (IGT), in which postprandial glucose control is impaired, and/or impaired fasting glucose (IFG) which is characterized by a chronic elevation of fasting plasma glucose (FPG).

In the literature (ADA, 2017; Buysschaert, 2011), an increased HbA1c of 5.7 to 6.4% is also identified as a criterion for prediabetes.

The blood glucose criteria described in the following Table 1 for diagnosing prediabetes are given in the literature (e.g. ADA, 2017; Nathan, 2007; Buysschaert, 2011; Ryden, 2013). The same or very similar definitions of IFG, IGT and HbA1c were also used in the DPP (DPP, 2002) and DPPOS. While the WHO guidelines (WHO 2006) use a different definition for the lower level of FPG in the definition of IFG (110mg/dl), the WHO definition of IGT is identical to that proposed by ADA and AACE.

Table 1 Classification of glucose tolerance states

State	FPG level mg/dl (mmol/l)	2-h plasma glucose in OGTT mg/dl* (mmol/l)	HbA_{1C} (%)
Normal glucose tolerance	<100 (<5.6)	<140 (<7.8)	<5.7
Prediabetes			
IFG	100–125 (5.6-6.9)	---	---
IGT	---	140-199 (7.8-11.0)	---
Combined IFG/IGT	100–125 (5.6-6.9)	140-199 (7.8-11.0)	---
Increased HbA_{1C}	---	---	5.7-6.4
Type 2 diabetes	>125 (>6.9)	>199 (>11.0)	>6.4

*Standard 75-g OGTT; FPG=fasting plasma glucose; NGT=Normal glucose tolerance; OGTT=oral glucose tolerance test

Besides FPG and HbA1c as diagnostic criteria for prediabetes, OGTT may be important in order not to overlook prediabetes in overweight or obese patients (Cosson, 2010).

Both impaired glucose tolerance and impaired fasting glucose, despite representing two heterogeneous conditions with different underlying mechanisms and natural history, which only partially overlap (Faerch, 2009; Meigs, 2003; Nathan, 2007), are insulin resistant states.

In both cases, the magnitude of the disturbances in glycemic function is insufficient to support a diagnosis of type 2 diabetes. HbA1c in prediabetes is below 6.5%. As soon as IFG>126mg/dl, and/or IGT>200mg/dl and/or HbA1c>6.5%, the prediabetic status has converted to overt diabetes (ADA, 2017).

Hereafter, the term "prediabetes" includes IGT and/or IFG and/or HbA1c of 5.7 to 6.4%.

Incidence and prevalence

Recent analyses show that not only the prevalence of type 2 diabetes is increasing, but the prevalence of prediabetes is strongly increasing as well.

Three population-based observational cohorts in the USA showed that prediabetes was prevalent among the population (Rhee, 2010). It has been estimated that one in four adults in the US has prediabetes (Bergman, 2011). The International Diabetes Federation projected that 7% of the world's population, comprising almost 400 million individuals, will have IGT by the year 2030 (IDF, 2012). Prevalence estimations for IGT for Central and South America are 7.5%, for the Middle East 8.2%, and for South East Asia 6.2% (Colagiuri, 2011).

Table 2 Prevalence of prediabetes in different countries

Country	Reference	Prevalence (%)
Brazil	Nascimento de Matos, 2011	68 (high risk patients)
China	Xu, 2013	50.1 (cross-sectional study)
UK	Mainous, 2014	35.3 (cross-sectional study)
India	Anjana, 2011	8.1-14.6 (urban and rural areas)
Indonesia	Soewondo, 2011	IGT 10% (cross-sectional study)
Malaysia	Mustafa, 2011	19.5 (cross-sectional study)
Saudi Arabia	Bahijri, 2016	9.0 (Saudi and non-Saudi in Jeddah)
Singapore	Wong, 2016	15.5 (dynamic Markov model)
South Africa	Erasmus, 2012	15.3 (coloured population)
USA	Rhee, 2010 McKeefer, 2013	33 in SIGT*, 38 in NHANES* III, 36 in NHANES 2005-2006 36.2 (nationally representative sample)

*SIGT = Screening for Impaired Glucose Tolerance; NHANES = National Health and Nutrition Examination Survey.
An estimated 850,000 people in the UK may have diabetes but are not diagnosed. Many more may have blood glucose levels above the normal range, but not high enough for a diabetes diagnosis (NICE, 2012). Around 1 in 7 adults may have either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), based on World Health Organization (WHO) criteria (NICE, 2012). According to recent literature, the prevalence of prediabetes in the UK (Mainous, 2014) and the US (Rhee, 2010; McKeefer, 2013) are very similar.

Risk factors

The risk factors for the development of prediabetes are basically the same as for diabetes (ADA, 2017; IDF, 2015). It has also been suggested that prediabetes can be considered as mild diabetes (Ferrannini, 2014).

Therefore, the most important complication of prediabetes is the continued deterioration of glucose tolerance to diabetes:

Individuals with prediabetes are at high risk for the development of diabetes mellitus. The American Diabetes Prevention Program (DPP) already showed in 2002 that approximately 10% of individuals with impaired glucose tolerance developed diabetes on an annual basis (Knowler, 2002). According to published clinical data, some 70% of individuals with untreated IFG and/or IGT will eventually go on to develop clinical type 2 diabetes (Bergman, 2011; Nathan, 2007). Interestingly, patients diagnosed with both impaired fasting glucose and impaired glucose tolerance appear to have an increased risk of developing diabetes when compared to individuals with isolated impaired fasting glucose or impaired glucose tolerance (Moutzouri, 2011).

It is furthermore known that prediabetes is associated with an increase in the risk of adverse cardiovascular outcomes (Barr, 2007; Coutinho, 1999; DECODE 2001; Magliano, 2010; Ryden, 2013).

Mortality

Individual-level evidence from prospective studies suggests that fasting hyperglycemia, post-load glucose, and HbA1c are all robust predictors of vascular mortality (Barr, 2007; DECODE, 2001; Sarwar, 2010) and, according to multivariable adjusted analyses, these associations are independent of vascular risk factors such as obesity, blood pressure, triglyceride, and lipoproteins (The Emerging Risk Factors Collaboration, 2010; Seshasai, 2011; Brunner, 2006).

Type 1 Diabetes

Type 1 diabetes mellitus (T1DM) is caused by an autoimmune reaction, in which the body's defense system attacks the insulin-producing beta cells in the pancreas. As a result, the body can no longer produce the insulin it needs. Why this occurs is not fully understood. The disease can affect people of any age, but onset usually occurs in children or young adults (IDF, 2015).

Incidence and prevalence

Data from large epidemiologic studies worldwide indicate that the incidence of T1DM has been increasing by 2–5% worldwide and that the prevalence of T1DM is approximately 1 in 300 in the US by 18 years of age. An initial report of the DIAMOND project (Karvonen, 2000) described the incidence of T1DM in children ≤14 years of age in 50 countries worldwide totaling 19,164 cases from a population of 75.1 million children (an estimated 4.5% of the world's population in this age range) from 1990–1994. A greater than 350-fold difference in the incidence of T1DM among the 100 populations worldwide was reported with age-adjusted incidences ranging from a low of 0.1/100,000 per year in China and Venezuela to a high of 36.5/100,000 in Finland and 36.8/100,000 per year in Sardinia. The lowest incidence (<1/100,000 per year) was reported in the populations from China and South America and the highest incidence (>20/100,000 per year) was reported in Sardinia, Finland, Sweden, Norway, Portugal, the UK, Canada, and New Zealand.

T1DM is the major type of diabetes in youth, accounting for ≥85% of all diabetes cases in youth < 20 years of age worldwide. In general, the incidence rate increases from birth and peaks between the ages of 10–14 years during puberty (Maahs, 2010): Few studies on epidemiology of T1DM in adults are available worldwide, as compared to those reporting on children with T1DM (Diaz-Valencia, 2015), and the ADA states that the exact number of individuals with type 1 diabetes around the world is not known, but in the U.S., there are estimated to be up to 3 million (Chiang, 2014).

Risk factors

T1DM is the result of a combination of genetic and environmental influences. It most commonly results from autoimmune destruction of insulin-producing b-cells in the pancreas (Shulman, 2010). Eisenbarth (Devendra, 2004) proposed that one or more environmental factors, such as enteroviruses, dietary factors or toxins, might trigger the development of T-cell dependent autoimmunity in genetically susceptible individuals. Usually, these patients are also susceptible to other autoimmune diseases such as Hashimoto, Addison and coeliac disease (Shulman, 2010).

Genetic factors include a susceptibility predominantly in the HLA genotypes DR and DQ, and to a lesser extent in a host of other genetic loci termed IDDM (insulin-dependent diabetes mellitus) susceptibility genes. The HLA locus is thought to confer about 50% of the genetic roughly 15% from two other genes, insulin-VNTR (IDDM2) and CTLA-4 (IDDM12), with minor contributions from the other IDDM genes (Daneman, 2006).

Chronic complications of type 1 diabetes (see type 2 diabetes) such as retinopathy, nephropathy, and neuropathy have rarely been reported in prepubertal children and children with diabetes duration of only 1–2 years; however, they may occur after the onset of puberty or after 5–10 years of diabetes (Cho, 2011). In adulthood, the complications of type 1 diabetes do not differ from those for type 2 diabetes. But in addition, ADA (2014) describes several co-existing autoimmunity diseases, including coeliac disease and thyroid disease.

Mortality

Historically, T1DM has been associated with a significant reduction in life expectancy (Livingstone, 2015). Diabetes charities such as Diabetes UK and the Juvenile Diabetes Research Foundation cite losses of life expectancy of between 15 and 20 years in T1DM (both via Livingston, 2015). In the recent analysis by Livingstone (2015) found an average loss of 11.1 years in men and 12.9 years in women. The relationship of different causes of death varied by age, with acute complication such as diabetic coma or diabetic ketoacidosis being the largest cause of the loss in life expectancy younger than age 50 years, followed by ischemic heart diseases, which become more important with longer life. Renal function loss was also contributing to the increased relative risk of death. The Yorkshire Register of Diabetes in Children and Young People found that there is no improvement in mortality rates for deaths attributable to acute complications (Evans-Cheung, 2018).

SI.2 Concomitant Medications in the Target Population

Type 2 diabetes

The primary effectiveness of T2DM treatment therapy is today usually determined by change in HbA1c (Stein, 2013), although being a surrogate outcome (Singh, 2014). ADA and EASD recommend lowering HbA1c to 7.0% to reduce incidence of microvascular disease. More stringent targets (e.g. 6.0–6.5%) might be considered in patients with short disease duration, long life expectancy, and no significant cardiovascular disease, if this can be achieved without significant hypoglycemia or other adverse effects. Less stringent goals, e.g. 7.5–8.0% or even slightly higher are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive education, counseling, or even very intensive treatment including insulin (ADA, 2017).

The first intervention in newly diagnosed diabetes is still a change in lifestyle together with weight loss and physical activity.

As of 2017, there are now 9 distinct oral pharmacologic classes and a variety of insulin and noninsulin injectable medications available for the treatment of T2DM (Tran, 2015). Metformin was established as first-line oral antidiabetic therapy in patients with T2DM by findings of the UKPDS study in 1998 and further confirmed in all internationally accepted guidelines (UKPDS 34, 1998; Nathan, 2009) unless contraindicated.

As T2DM is chronic progressive, many patients will eventually require treatment with multiple glucose-lowering medications (combination therapy). These include sulfonylureas, alpha-glucosidase inhibitors, meglinides, GLP-1 receptor antagonists, DPP4-inhibitors, SGLT-2 inhibitors, bile acid sequestrants, dopamine receptor antagonists and insulin (Tran, 2015).

Prediabetes

The first intervention in newly diagnosed diabetes is still a change in lifestyle together with weight loss and physical activity. ADA (2019) recommends only metformin for the treatment of prediabetes, as all other diabetes treatments lack sufficient clinical data in this patient group.

Treatment of comorbidities in prediabetic / diabetic patients

This patient group can suffer from several comorbidities, mainly cardiovascular and dyslipidemias (see section SI.3), such that the potential for the administration of concomitant medications is high.

Common concomitant medications may include statins, antihypertensives (including diuretics, beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor antagonists and calcium channel inhibitors), anti-coagulants, antianginals, and antibiotics, among others (Lin, 2015; Tabák, 2012). In addition, anti-obesity drugs, such as orlistat, may be used (Bansal, 2015).

Type 1 diabetes

As absolute deficiency of insulin is the root cause for Type 1 Diabetes, the treatment of choice is substitution of insulin.

SI.3 Important Co-morbidities Found in the Target Population

Prediabetes and T2DM

As may be expected with a chronic disease that primarily affects middle-aged and older individuals, T2DM is usually complicated by other medical conditions. In the 1999-2004 cohort of the National Health and Nutrition Examination Survey (NHANES), only 14% of patients with type 2 diabetes had no other comorbidities (Suh, 2010). It has also been suggested that prediabetes can be considered as mild diabetes, and progression rather than conversion describes the deterioration of glucose tolerance that leads to overt diabetes (Ferrannini, 2014). Therefore, the co-morbidities for prediabetes and diabetes can be considered the same:

Obesity

In the 1999-2004 NHANES study of people with type 2 diabetes, 27% of the participants were overweight (BMI 25–29 kg/m^2) and 61% were obese (BMI ≥30 kg/m^2) (Suh, 2010).

Dyslipidemia

AACE (Garber, 2017) and the American Diabetes Association (ADA, 2017) both recommend annual dyslipidemia screening by means of a fasting lipid profile for all adults with diabetes. A retrospective study of electronic medical records of over 125,000 patients with type 2 diabetes found that 99% of them were eligible for lipid-lowering therapy, but only 63% were receiving a statin (Fu, 2011). Moreover, in the NHANES 1999–2004 cohort, 46% of patients with type 2 diabetes had elevated lipid values, suggesting a need for improved identification and control of lipid abnormalities (Suh, 2010).

Hypertension

At least 67% of persons with T2DM either have uncontrolled hypertension or are being treated for elevated blood pressure (Suh, 2009). The combination of hypertension and diabetes magnifies the risk of diabetic complications, while treatment of hypertension decreases both microvascular and macrovascular risk. In the United Kingdom Prospective Diabetes Study (UKPDS), each 10 mm Hg decrease in systolic blood pressure was associated with a 17% reduction in rates of diabetes-related mortality, a 12% reduction in myocardial infarction, and a 13% reduction in microvascular endpoints ($p<0.0001$) (UKPDS 36; UKPDS 38).

Chronic kidney disease

Chronic kidney disease (CKD) affects ~40% of patients with diabetes (Plantinga, 2010). It is not only a complication of diabetes; it is also frequently a comorbidity that is present before diabetes onset. In addition, CKD more than doubles the risk of CVD, whether or not patients have diabetes. The National Kidney Foundation (NKF) has issued comprehensive guidelines for the diagnosis and management of CKD in all patients and more specific recommendations for diabetic kidney disease (DKD) (Vassalotti 2007, NKF, 2007).

Cardiovascular disease

Cardiovascular disease (CVD) is the primary cause of death for most persons with diabetes, and modification of CVD risk factors is an essential component of the comprehensive care plan for all forms of diabetes. CVD encompasses cerebrovascular disease, coronary artery disease (CAD), and coronary heart disease (CHD) (AACE guideline, Garber 2016).

Depression

Routine depression screening of adults with diabetes is recommended. Untreated comorbid depression can have serious clinical implications because depression contributes to poor self-care, reduced treatment adherence, and poor glycemic control (Lustman, 2000). Depression and diabetes also are associated with a significantly increased all-cause and CVD-related mortality (Pan, 2011).

Sleep disorders

Sleep deprivation from any cause, and sleep apnea, aggravate insulin resistance, hypertension, hyperglycemia, dyslipidemia, and inflammatory cytokines. Sleep apnea, in which the individual stops breathing and is then awakened by the need for oxygen, is especially common in adults with diabetes, occurring in approximately 2 of 3 of men with diabetes older than 65 years (Tasali, 2008). The most common type of sleep apnea, obstructive sleep apnea, occurs most frequently in obese persons, men, and the elderly (Young, 2002). Treatment of obstructive sleep apnea in persons with diabetes can lower blood glucose levels as much or more than treatment with oral antidiabetic agents and can also improve cardiovascular outcomes (Kaneko, 2003).

Cancer

A growing body of evidence suggests that diabetes itself and some antidiabetic treatments may increase cancer risk (Giovannucci, 2010).

Type 1 diabetes

In type 1 diabetes, apart from the comorbidities related to the devices for insulin application, the overall effect of hyperglycemia is shared with type 2 diabetes. Acute complications also include diabetic coma or diabetic ketoacidosis (Livingstone, 2015), which is rarely seen in type 2 diabetes, although the latter has been reported as adverse reaction for SGLT-2 inhibitors, a class of type 2 diabetes medications (Fadini, 2017).

Part II: Module SII Non-Clinical Part of the Safety Specification

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicology[1]	
Single and repeat-dose toxicity Acute toxicity has been evaluated in different species (rodents and non-rodents). At very high doses the main toxic symptoms correspond to an activity reduction, ataxia and diarrhea Various chronic studies have been carried out in different species and over variable durations going up to 104 weeks. Metformin hydrochloride is well tolerated at doses up to 150 mg/kg/day in the mouse, 120 mg/kg/day in the rat, 50 mg/kg/day in the dog and 180 mg/kg/day in the monkey. At the highest dose, the main observed target organs/symptoms are the following: • in the mouse, an increase in kidney tubular dilatation and in tissue vacuolization incidence • in the rat, an increase of endometrial polyp incidence • in the dog, at doses of 100 mg/kg/day and above in the brain, heart, liver, and gastrointestinal tract • in the monkey, gastrointestinal tract (diarrhea, anorexia and vomiting)	Gastrointestinal disorders such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite may occur. A slow increase of the dose may also improve gastrointestinal tolerability.
Reproductive and developmental toxicity Animal studies do not indicate harmful effects with respect to fertility, pregnancy, embryo-fetal development, parturition or postnatal development; in rabbits a reduction in live births at maternally toxic doses with high safety factor, potential impact on sperm quality at very high concentrations.	Metformin data do not indicate harmful effects on fetal development, a large amount of data on pregnant women (more than 1000 pregnancy outcomes) from a register-based cohort study, published data (meta-analyses, clinical studies and registries) indicate no adverse effect on pregnancy or an increased risk of congenital abnormalities nor feto/ neonatal toxicity after exposure to metformin before conception and/or during pregnancy.
Nephrotoxicity An increase in tubular dilatation and in tissue vacuolization incidence with high doses in the mouse.	Not considered to be nephrotoxic in humans. As metformin is excreted by the kidney, creatinine clearance should be determined before initiating treatment and regularly thereafter, especially in elderly, renal impaired patients and those at risk of acute renal failure.
Hepatotoxicity Leukocytic infiltration of the hepatic sinusoids in the dog which was not considered to be associated with a specific hepatopathy	Not considered to be hepatotoxic in humans
Genotoxicity No evidence of a mutagenic potential was found in the in vitro and in vivo core battery tests.	Not considered to be genotoxic in humans
Carcinogenicity Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. There is no carcinogenic potential in either species studied	Not considered to be carcinogenic in humans

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety Pharmacology[1]	
No proprietary safety pharmacology studies in vivo and in vitro were performed with metformin	Extensive use in humans for >10 years has not identified a negative cardiovascular or neurological effect in humans.
Cardiovascular Myocardial fiber atrophy was observed in dogs in the high dose group (150 mg/kg/day)	
Neurological During in-life phase dogs with high doses showed central nervous system involvement and histopathologically cerebral edema, neuronal necrosis, and cerebral vascular changes animals treated with 100 and 150 mg/kg; Slight thickening of vascular walls was observed microscopically in 2 of 6 dogs in the 50 mg/kg/day group	

[1] Non-Clinical Overview, 2017; Toxicology Written Summary, 2017

Module SIII Clinical Trial Exposure

The total cumulative exposure to metformin from completed clinical trials and the enrolment/randomization schemes for ongoing trials is estimated to be at least 24,600 subjects. These numbers include 1,836 healthy volunteers. Detailed cumulative exposure per study type is provided in Table 3:

Table 3 Estimated Cumulative Subject Exposure to metformin, in clinical trials, which were ongoing or completed up to 01 Oct 2020, per study

Study ID		Number of Subjects Exposed*
Biopharmaceutical and pharmacokinetic studies		
89-11-6023	GIR	24
89-12-6023	GIR	18
CV138-021	GXR	16
CV138-026	GIR	16
CV138-028	GXR	16
CV138-035	GIR, GXR	53
CV138-038pk	GIR	32
CV138-072	GIR	28
MET-GB-89-HOCKA	GIR	16
MET-UK-98.01	GIR	12
MET-UK-98.02	GIR	16
MET-UK-98.03	GIR	16
MET-UK-99.01	GIR	16
RD 298-17142 (Simbec 1)	GIR	20
RD 298-17143 (Simbec 2)	GIR	18
Total subjects exposed to metformin in biopharmaceutical and pharmacokinetic studies		317

Study ID		Number of Subjects Exposed*
Clinical Pharmacology studies		
89-2B-6023	GIR	15
90-13-6023	GIR	36
91-03-6023	GIR	15
91-04-6023	GIR	18
91-05-6023	GIR	18
91-06-6023	GIR	18
92-01-6023	GIR	18
CV138-031	GXR	18
CV138-082	GXR	22
CV138-085	GXR	26
CV138-087	GXR	24
CV138-088	GXR	36
CV138-098	GXR	28
CV138-099	GXR	28
EML 019502-H101	Stagid, GIR	24
EML 056023-H101	GXR	33
EML 056023-H102	GXR	32
EML 056023-H103	GXR	22
EML 056023-H104	GXR	22
EML 076023-H105	GXR	24
EML 076023-H106	GXR	24
EMR 200084-107	GXR	49
EMR 200084-108	GXR	78
EMR 200084-109	GXR	78
MS200084_0009	GIR	44
MS200084_0013	GXR	54
Total subjects exposed to metformin in bioequivalence studies		**804**
Controlled clinical trials		
87-1D-6023	GIR	289
87-2D-6023	GIR	632
89-1C-6023	GIR	604
CV138-001	GIR	451
CV138-010	GXR	235
CV138-010 open label extension	GXR	88
CV138-012	GXR	217
CV138-012 open label extension	GXR	180
CV138-016	GIR	39
CV138-020	GIR	20
CV138-036	GXR	742
CV138-036 open label extension	GXR	666

Study ID		Number of Subjects Exposed*
CV138-038	GIR	106
CV138-039	GIR	82
CV138-039 open label extension	GIR	67
CV138-045	GIR	14
CV138-097	GXR	371
CV181-206	GIR, GXR	568
EMR200084-508	GIR	0
EMR200084-513	GIR, GXR	532
MET-AM-84-DORF1	GIR	51
MET-AM-86-DORF2	GIR	50
MET-AM-88-DUCHI	GIR	61
MET-D-86-BERGI	GIR	97
MET-GB-85-DORNA	GIR	62
MET-GB-86-CAMP1	GIR	50
MET-S-86-HERMA	GIR	144
UKPDS	GIR	753
Total subjects exposed to metformin in controlled clinical trails		**7171**
MET-D-86-HAUPT	GIR	3724
MET-AM-87-PHASE	GIR	4374
Total subjects exposed to metformin in uncontrolled clinical trials		**8098**
Total subjects exposed to metformin in safety studies		
CV138-002 COSMIC	GIR	>9000
Total subjects exposed to metformin		**> 25,390**

Most clinical studies sponsored by the Company were conducted many years ago, therefore the available information is limited, and it is not possible to accurately provide the number of patients included in each group nor additional stratification of exposure data by age / sex or racial group.

Module SIV Populations not Studied in Clinical Trials

This section is omitted based on GVP module V (Rev 2), Section V.C.1.1.5 (well established medicinal product) and section V.C.2.1.

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

Not applicable (see above).

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

Not applicable (see above).

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

Not applicable (see above).

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

The patient exposure has been calculated using sales data and considering the mean Defined Daily Dose (DDD). The assumptions made for the DDD has varied during the life-cycle of this product. The current mean Defined Daily Dose is estimated to be 2 units per day. The number of patient years was calculated using the formula: (Number of tablets/2)/365.

Total non-study exposure has been calculated from review of previous PSURs for metformin salts as per the table below.

These data exclude the comparatively small amount of exposure to metformin chlorophenoxyacetate, which was only marketed in France and was discontinued in 2002.

The total patient exposure to metformin since 1996 is estimated at 196,437,487 patient years.

SV.1.2 Exposure

Table 4 Cumulative Patient Exposure to metformin up to 01 Oct 2020

Review period	Salts	Total exposure (patient-years)
01 Jan 2006 to 01 Apr 2009	Metformin embonate	571,622
01 Jan 1996 to 31 Jan 1999	Metformin hydrochloride	10,227,000
01 Feb 1999 to 31 Dec 1999	Metformin hydrochloride	4,313,688
01 Jan 2000 to 31 Mar 2001	Metformin hydrochloride	7,122,665
01 Apr 2001 to 31 Mar 2002	Metformin hydrochloride	7,250,000
01 Apr 2002 to 31 Mar 2003	Metformin hydrochloride	4,438,440
01 Apr 2003 to 31 Mar 2004	Metformin hydrochloride	5,358,724
01 Apr 2004 to 31 Mar 2005	Metformin hydrochloride	4,8443,054
01 Apr 2005 to 31 Mar 2006	Metformin hydrochloride	6,173,969
01 Apr 2006 to 31 Mar 2007	Metformin hydrochloride	8,132,939
01 Apr 2007 to 31 Mar 2008	Metformin hydrochloride	7,396,707
01 Apr 2008 to 01 Apr 2009	Metformin hydrochloride	7,260,366
02 Apr 2009 to 01 Apr 2010	Metformin hydrochloride, embonate, chlorophenoxyacetate	13,879,071
02 Apr 2010 to 01 Apr 2011	Metformin hydrochloride, embonate, chlorophenoxyacetate	8,942,030
02 Apr 2011 to 01 Apr 2012	Metformin hydrochloride, embonate, chlorophenoxyacetate	4,141,763
02 Apr 2012 to 01 Apr 2015	Metformin hydrochloride, embonate	22,882,719
02 Apr 2015 to 01 Apr 2016	Metformin hydrochloride, embonate	10,556,046
02 Apr 2016 to 01 Apr 2017	Metformin hydrochloride, embonate	10,437,932
02 Apr 2017 to 01 April 2018	Metformin hydrochloride, embonate	12,704,475
02 Apr 2018 to 01 Apr 2019	Metformin hydrochloride, embonate	14,617,712
02 Apr 2019 to 01 Apr 2020	Metformin hydrochloride, embonate	16,680,559
02 April 2020 to 01 Oct 2020	Metformin hydrochloride, embonate	8,506,006
Cumulative Total exposure		**196,437,487**

Module SVI Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The prescription of metformin hydrochloride (Glucophage®) and metformin embonate (Stagid®) is limited to healthcare professionals. This compound has no neurological activity that may induce a misuse for illegal purposes. Thus, the potential for misuse for illegal purposes is low.

Module SVII Identified and Potential Risks

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

Not applicable as this RMP version is not the initial submitted RMP.

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

No new safety concern was identified since last approval of the RMP in March 2020.

However, revision of the missing information 'pregnancy and lactation' was triggered by the completion of the PASS CLUE and subsequent compilation of the published clinical evidence.

The missing information was revised to: "Long-term offspring outcomes after exposure to metformin in utero".

"Lactation" was removed from the list of safety concerns as no additional pharmacovigilance activities or additional risk minimization measures have been conducted or are planned for this risk, and future feasible pharmacovigilance activities probably would not characterize the risk further or change the safety profile of the product for this specific population. Moreover, as per GVP Module V (rev. 2, dated March 2017) Risk Management System, the absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern.

As per section "Pregnancy and lactation" of the currently approved product information, metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk of adverse effects in the child.

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

Important Identified Risk:

Lactic acidosis including:

- use in patients with renal dysfunction with GFR < 45 ml/min
- concomitant use of iodinated contrast media

The MAH decided to discuss the use of metformin in patients with a renal dysfunction (GFR < 45 ml/min) or with concomitant use of iodinated contrast media as part of the overarching important identified risk **Lactic acidosis.** Both, renal dysfunction below GFR < 45 ml/min and concomitant use of iodinated contrast media are not independent risks but important risk factors for metformin accumulation due to lack of adequate metformin renal excretion, which might trigger, contribute to or fortify lactic acidosis.

Definition of lactic acidosis:

Lactic acidosis is defined as blood lactate concentration of > 5mmol/l and arterial pH<7.35 (de Groot, 2011).

Lactic acidosis can be stratified by its cause (Cohen, 1976):

- Type A lactic acidosis: Clinical Evidence of Inadequate Tissue Oxygen Delivery
- Type B lactic acidosis: No Clinical Evidence of Inadequate Tissue Oxygen Delivery
  - Associated with underlying diseases (e.g. ketoacidosis, leukemia, lymphoma, AIDS)
  - Associated with drugs & toxins (e.g. phenformin, cyanide, beta-agonists, methanol, nitroprusside infusion, ethanol intoxication in chronic alcoholics, anti-retroviral drugs)
  - Associated with inborn errors of metabolism (e.g. congenital forms of lactic acidosis with various enzyme defects such as pyruvate dehydrogenase deficiency)

Potential mechanism of lactic acidosis:

Type A lactic acidosis, such as acute cardiovascular events, liver cirrhosis, and sepsis are all associated with an increased mortality risk.

In the event of hypoxia, the mitochondria are unable to continue adenine triphosphate (ATP) synthesis at a rate sufficient to supply the cell with the required ATP. In this situation, glycolysis is increased to provide additional ATP, and the excess pyruvate produced is converted into lactate and released from the cell into the bloodstream, where it accumulates over time. While increased glycolysis helps compensate for less ATP from oxidative phosphorylation, it cannot bind the protons resulting from ATP hydrolysis. Therefore, proton concentration rises and causes acidosis.

In a review on cases of metformin-associated lactic acidosis by Stades (2004), all patients had at least one risk factor (cardiovascular events, pulmonary failure, hepatic failure, alcohol excess, or sepsis) for the development of lactic acidosis, independent of metformin use.

Metformin-induced lactic acidosis is a type B lactic acidosis. Metformin can bind to complex 1 of the mitochondrial electron transport chain (Gomez, 2019). Alternatively, it has been postulated that metformin blocks gluconeogenesis, thereby decreasing conversion of lactate to glucose (Lalau, 2015), and that it promotes intestinal anaerobic glycolysis with increased lactate production (Krowl, 2018).

- Potential mechanism for the development of lactic acidosis in patients with renal dysfunction with GFR < 45 ml/min:

Lactic acidosis results from two mechanisms. One is lactate overproduction (e.g. tissue hypoxia in type A lactic acidosis and metformin-accumulation in type B lactic acidosis) and the other is lactate underutilization. The liver and kidney are primary lactate metabolizers, accounting for ~60% and ~30% of lactate clearance, respectively (DeFronzo, 2016). Especially, this lactate underutilization seems to decide the prognosis of the patients with lactic acidosis (Ando, 1990). Existing kidney disease appears to be amongst the most potent predictor of acute decline in kidney function (Hsu, 2008).

Acute or severe renal impairment therefore presents a risk factor for metformin-associated lactic acidosis (MALA) in both ways: Metformin is eliminated almost exclusively through the kidneys via combined glomerular filtration and tubular secretion (Scheen 1996, Lipska 2011). Thus, the inability to clear metformin efficiently (Lipska, 2011) increases the risk of metformin accumulation with subsequent increased lactate production. Secondly, the condition of acute or severe renal failure decreases lactate utilization and clearance.

- Potential mechanism for the development of lactic acidosis in patients with concomitant use of iodinated contrast media:

Intravascular administration of iodinated contrast media can result in contrast-induced nephropathy (CIN) (Nicola, 2015). The pathophysiology of contrast-induced nephrotoxicity has not been fully characterized, but possible mechanisms include osmotic-mediated changes in renal hemodynamics (decreased renal blood flow with subsequent renal ischemia) and direct tubular injury from the contrast molecule-specific chemotoxicity (Rose, 2015).

As described above, acute or severe renal failure in a metformin-treated patient increase the risk of lactic acidosis in a multifactorial way.

Evidence sources and strength of evidence:

Several sources provide evidence on lactic acidosis, which is a serious condition with a mortality rate of around 25% if not treated promptly (Renda, 2013): Spontaneous case reports from the post-marketing experience; scientific medical literature, such as Bodmer 2008, Mani 2009, Salpeter 2010, and Scarpello 2008 among others.

In the large, updated Cochrane meta-analysis on the risk of fatal and nonfatal lactic acidosis (LA) with metformin use in T2DM, Salpeter (2010) pooled data from 347 comparative trials and cohort studies in diabetic patients treated with different hypoglycemic drugs, with 70,490 patient-years of metformin use and 55,451 patients-years in the non-metformin group, not a single case of lactic acidosis was found. In a large, nested, case-control analysis of the UK general practice research database (Bodmer, 2008), the crude incidence of lactic acidosis was even lower at 3.3 cases per 100,000 person-years among metformin users (with different stages of renal impairment). Relevant co-morbidities known as risk factors for lactic acidosis could be identified in all case subjects (Mani, 2009).

Characterization of the risk:

Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be immediately hospitalized as it is a serious condition with a high mortality if not treated promptly.

Frequency of lactic acidosis:

In the largest analysis so far, Salpeter (2010) pooled data from 347 comparative trials and cohort studies in diabetic patients treated with different hypoglycemic drugs. Not a single case of lactic acidosis was found in >70,000 metformin patient-years. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency, but patient-level serum creatinine concentrations were not always available for review. Based on statistical inference, the estimated upper limit of true incidence was **4.3 and 5.4 cases per 100,000 patient-years** in the metformin and non-metformin groups, respectively.

In the large, nested, case-control analysis of the U.K. General Practice Research database, the crude incidence of lactic acidosis was even lower at **3.3 cases per 100,000 person-years** among metformin users and 4.8 cases per 100,000-person years among sulfonylurea users (Bodmer, 2008). As previously reported, the incidence of LA or hyperlactatemia in current metformin users was **7.4** (95% CI: 5.6-9.63) **per 100,000 person-years** according to Eppenga (2014), and the incidence of LA **10.37 per 100,000 patients-years** in metformin users (Richy, 2014).

Relevant co-morbidities known as risk factors for lactic acidosis can usually be identified in all subjects (Mani, 2009). In a retrospective analysis by Goncalves (2013), all patients presenting with lactic acidosis on admission to an intensive care unit (ICU) between 2010 and 2013 presented with acute renal failure (73%) or severe sepsis (27%). The authors concluded that the accumulation of metformin may coexist with other risk factors, and every factor contributes to the pathogenesis of lactic acidosis.

A retrospective database analysis of patient records from the Clinical Practice Research Datalink (CPRD) in the period of 01 January 2007 to 31 December 2012 (6 years) in all patients with type 2 diabetes mellitus that had at least one measure of GFR or chronic kidney disease (CKD) was performed. Incidence rates for patients in different stages of CKD were compared among patients using metformin versus those using other anti-diabetic drugs or no treatment. Both fatal and non-fatal lactic acidosis cases were examined. The final study population of eligible patients included 134,956 patients. Of these patients, 77,601 were treated with metformin. Of these metformin patients, 50% had mildly reduced kidney function, 40.3% moderately reduced. 1.9% severe and 7.8% normal kidney function. There were 35 lactic acidosis events (10.37 per 100,000 patient years 95% CI 7.22-14.42) in metformin treated patients. None of the lactic acidosis events were fatal. 23 lactic acidosis events occurred in patients with moderate renal impairment treated with metformin. The absolute number of lactic acidosis events in patients with moderate renal impairment that were older and had a longer duration of diabetes than those with no or mild renal impairment was slightly higher compared with normal renal function or mild renal impairment but the p values of the incidence rates in both the Chi Square Test as well as Fisher Exact Test did not

show any significant difference. There was no significant difference in the incidences of lactic acidosis with metformin compared to other oral antidiabetic agents or compared with no treatment. Of the 23 patients with moderate renal impairment for whom a lactic acidosis event was described on metformin treatment, 16 had conditions such as acute kidney failure, ischemic heart disease, and acute heart failure that could place them at an increased risk for lactic acidosis independent of metformin use (Richy, 2014).

Frequency of lactic acidosis in Global Safety database (cumulatively 01 October 2020):

From the cumulative review of the Company's Global Safety Database, 5,136 cases within the SMQ lactic acidosis were retrieved. Cumulative reporting incidence until cut-off date of this report (01 October 2020) is calculated as **2.61 in 100,000 patient years**, based on the MedDRA SMQ Lactic acidosis broad scope. A total of 1,050 of all valid cases had a fatal outcome (corresponding to 20.4% of cumulative cases of lactic acidosis). 391 cases were non-serious and 4,745 serious.

Risk factors and risk groups:

Reported cases of lactic acidosis with metformin have occurred primarily in diabetic patients with acute renal failure or prodromal events.

The main risk factor for acute renal impairment as identified by many authors, are diarrhea and vomiting (Rhee, 2017; Bell, 2017). In addition, risk factors include alcohol intake, especially in higher amounts, contrast-induced nephropathy (see below) and drugs / drug classes associated with acute renal impairment (Pazhayattil, 2014; McWilliam, 2007; Markowitz, 2005) such as antihypertensive therapy (including ACE inhibitor, angiotensin II receptor blocker), diuretics, NSAID (including paracetamol), antibiotics, antiviral, antifungal, oncologic drugs, radiocontrast, calcineurin inhibitors, lithium, H2-blocker, statins, gout medication and SGLT2-inhibitors. Further risk factors are poorly controlled diabetes, ketosis, prolonged fasting, severe infection, hepatic insufficiency, dehydration (i.e. severe diarrhea or vomiting) and any conditions associated with hypoxia (such as acute heart failure, acute myocardial infarction) (Lalau, 2010).

As mentioned above one of the main risk factors for lactic acidosis is the intravascular administration of iodinated contrast materials in radiologic studies which can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Therefore, depending on the renal function, metformin must be discontinued 48 hours before the test or from the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

Preventability:

Avoidance of the risk factors detailed above is the most effective preventive measure to avoid lactic acidosis:

Renal failure: Patients and/or care-givers should be informed of the risk and the symptoms of lactic acidosis and situations where renal function may become acutely impaired in order that patients can take preventative action and also are aware to seek medical advice should they experience any symptoms suggestive of the risk factors.

The patient should also be provided with information regarding the risk factors and the seriousness of lactic acidosis in the patient information leaflet.

Special caution is needed in situations where renal function may become acutely impaired, for example due to dehydration (severe or prolonged diarrhea or vomiting), or when initiating drugs which can acutely impair renal function (such as anti-hypertensives, diuretics and NSAIDs). In the acute conditions listed, metformin must be immediately and temporarily discontinued.

It is possible and recommended that the incidence of lactic acidosis can be reduced by assessing other associated risk factors, e.g. poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (Lalau, 2010).

The "use in patients with renal dysfunction with GFR < 45 ml/min" is adequately described in different sections of the product information such as "Posology and method of administration", "Contraindications", "Warnings and precautions". The risk of lactic acidosis might be minimized if the conditions described in "Contraindications", "Warnings and precautions" and "Posology and method of administration" are strictly followed and metformin is stopped if GFR drops below 30 ml/min.

Concomitant use of iodinated contrast media: Also, the "concomitant use of iodinated contrast media" is adequately described in sections "Posology and method of administration", "Contraindications", "Warnings and precautions" and "Interactions" of the product information.

Impact on the benefit-risk balance of the product:

The major risk factors of lactic acidosis as described above are explicitly specified in the respective SmPCs for metformin in sections "Contraindications", "Warnings and precautions", "Interactions", "Adverse reactions".

In stable moderate renal impairment (CKD stage 3), the benefit-risk of metformin is considered positive when the respective dose adaptions are applied.

In *patients with a GFR <30ml/min*, the benefit/risk of metformin is not considered positive at this point of time, even if the dose is further reduced in comparison to the recommendations in CKD stage 3, as recommended e.g. by Al-Hwiesh (2017) or Gopinath (2016), as long-term data on efficacy, even with further reduced maximum daily dose, are scarce.

Concomitant use of iodinated contrast media: It is recommended to halt metformin treatment in patients undergoing procedures involving iodinated contrast media, which is considered the most effective measurement of avoiding metformin accumulation in case of CIN.

Public health impact:

All cases of lactic acidosis require hospitalization and may also require intensive care with the associated inpatient costs. Lactic acidosis is a serious condition with high mortality if not treated promptly. Patients may present initially with non-specific symptoms and signs such as muscle cramps, abdominal pain or severe asthenia which can then rapidly progress to acidotic dyspnea, hypothermia and coma. If metabolic acidosis (e.g. ketoacidosis or lactic acidosis) is suspected, metformin must be discontinued, and the patient must be immediately hospitalized.

There is no substantial impact if metformin is administered according to the guidelines and the prescription information regarding dose limitation in moderate renal impairment, and the contraindication in GFR<30ml/min as well as in relation to administration of iodinated contrast media are followed.

SVII.3.2 Presentation of the Missing Information

Missing information: Long-term offspring outcomes after exposure to metformin in utero

Evidence source:

Diabetes mellitus throughout pregnancy is an increasing health problem in all developed and developing societies, steadily rising in prevalence (Klein, 2015). Globally, the number of live births affected by maternal hyperglycemia totals 20.4 million (IDF, 2019). There are three main conditions, in which metformin is increasingly used, namely pre-gestational diabetes mellitus (PGDM), gestational diabetes mellitus (GDM) and insulin-resistant polycystic ovary syndrome (IR-PCOS).

Pre-gestational diabetes mellitus (PGDM), namely diabetes existing prior to conception (Egan, 2015), is a chronic progressive disease and therefore requires continuous treatment throughout the pregnancy. Depending on the demographics of the population and the screening process used, around 1% of all pregnancies are in women with preexisting diabetes (Shub, 2020). In the past 20 years, the prevalence of PGDM has more than doubled (Feig, 2014), driven primarily by a younger age of onset and by an increasing prevalence of maternal obesity (Santos, 2019).

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with a first recognition or onset during the pregnancy. Of all types of diabetes, GDM accounts for approximately 90–95% of all cases of hyperglycemia in pregnancy (Ashwal, 2015) and up to 25% of pregnancies worldwide (Melchior, 2017). In Europe, a meta-analysis of studies published up to May 2016, assessed the overall prevalence of GDM as 5.4% (3.8–7.8) of all pregnancies (Eades, 2017). This was in line with the prevalence of GDM observed in latter nationwide studies: around 4.4% in Croatia (Vince, 2021), and 5.0% in Spain (López-De-Andrés, 2020). Other, nationwide studies also highlight some regional disparities, with a prevalence lower than 3% in Norway (Behboudi-Gandevani, 2021), Sweden (Hildén, 2020) or Denmark (Jeppesen, 2017); while around 7.5% in Poland (Wierzba, 2017).

One of the key features of PCOS is hyperglycemia or prediabetes caused by insulin-resistance. Metformin is increasingly used off-label for the use in PCOS. These women, who are usually of childbearing age, may use metformin and do not yet know that they are pregnant. Additionally, there is a growing number of patients who receive metformin off-label in some parts of the world for improvement of conception, predominantly in PCOS and continue the medication until the end of first trimester or throughout pregnancy (Begum, 2009).

PCOS affects 6-10% of all reproductive-aged women. PCOS increased the rate of infertility by 15 times, and the rate of early loss is 3 times greater (National Health Statistics, 2015; McDonnell, 2017).

A conservative estimation is therefore that at least 10% of all pregnancies are affected by one of these three hyperglycemic conditions worldwide.

It is well known that maternal diabetes itself significantly increases the risk of congenital malformations, fetal death, and spontaneous abortions.

Metformin has occasionally been used in pregnancy since the 1970s (Coetzee, 1979). In recent years, metformin has been used more and more for the treatment of insulin resistance and hyperglycemia during pregnancy. In an analysis of patient data from diabetic practices in Germany, the proportion of pregnant women receiving metformin prescriptions increased from 1.6% in 2008 to 5.3% in 2012 ($p<0.001$) (Heilmaier, 2014). According to Akinci (2010), metformin was even used in 17.7% of all GDM pregnancies in 2007. In a large cohort of over 10,000 individuals with GDM requiring medical therapy in the US, Caughey (2021) found that from 2015 to 2018, the use of metformin increased from 17% to 29%.

In recent years, medical treatment guidelines have been recommending metformin as alternative, addition or second line treatment, especially in GDM and PCOS (see Table 5)

Table 5 Metformin recommendation as per medical treatment guidelines

Guideline	Use	Recommendation summary
ADA 2020	**GDM**	Metformin is recommended as 2nd line treatment due to lack of long-term safety in the offspring.
	PCOS	Metformin should be discontinued at the end of the 1st trimester.
Queensland 2020	**GDM**	Metformin is an accepted treatment.
NICE 2020	**GDM** **PCOS**	Metformin is first line for treatment if blood glucose targets are not met within 2 weeks of dietary and lifestyle modifications. Metformin may be used in the periconception period and during pregnancy.
IDF 2019	**PGDM** **GDM**	Women who are taking metformin need to have the potential advantages and disadvantages of this medication outlined. Extensive clinical experience with the use of metformin in pregnancy over more than a quarter of a century is available […] with the proviso that it is not licensed for these indications.
ACOG 2018	**GDM**	Metformin is a reasonable alternative to insulin in people who decline or cannot afford insulin.
SMFM 2018	**GDM**	Metformin is a reasonable and safe first line alternative to insulin, recognizing that one-half of women will still require insulin to achieve glycemic control.
FIGO 2015	**GDM**	Metformin is a safe and effective 1st line therapy during 2nd and 3rd trimester. Insulin is the first line treatment in severe cases of GDM.
ES 2013	**GDM**	Metformin is to be used only for those women with gestational diabetes who do not have satisfactory glycemic control despite medical nutrition therapy and who refuse or cannot use insulin and are not in the first trimester.

In their recent guideline summary, Tsakeridis (2021) summarizes that "*there is a controversy among the reviewed guidelines on the first- and the second-line pharmacological treatment of GDM. Hence, whereas the ACOG, ADA, and the Endocrine Society (ES)(Blumer, 2013) recommend the use of insulin when glycemic targets are not achieved with diet and exercise, the NICE and the FIGO suggest the addition of metformin when lifestyle changes alone fail to maintain euglycemia, as 2 meta-analyses of 2015 proved that it performs slightly better than insulin and reduces several adverse maternal and neonatal outcomes (Li, 2015; Balsells, 2015).*

Furthermore, 3 recent meta-analyses proved that metformin yields equivalent outcomes to insulin regarding the reduction of maternal and perinatal complications (Farrar, 2017; Poolsup, 2014; Brown, 2017). […] However, the ACOG, ADA, and the ES state that this oral antidiabetic agent should be considered as a reasonable choice only for women who cannot accept, afford, or safely administer insulin therapy."

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) from a register-based cohort study (CLUE, see below), published data (meta-analyses, clinical studies and registries) indicate no increased risk of congenital abnormalities or feto/neonatal toxicity after exposure to metformin before conception and/or during pregnancy.

Population in need of further characterization:

Long-term safety data in offspring exposed to metformin during pregnancy are limited:

To close this information gap, Merck conducted, together with EPID® research, a retrospective analysis on the development of children born to mothers treated with metformin during pregnancy in Finland (**CLUE study, EMR200084_0011, EUPAS19686**):

The aim of this study was to investigate the long-term and immediate effects of exposure to metformin in utero among the children of all pregnant women treated with metformin, regardless of the purpose of the use. The analyzed long-term effects include diagnoses of obesity, hypoglycemia, hyperglycemia, hypertension, diabetes mellitus, and PCOS (girls only), diagnoses related to challenges in motor-social development, and growth outcomes, all from the age of one week and for as long as data are available. In addition, immediate effects of exposure to metformin in utero were investigated, including growth outcomes at birth, preterm birth, perinatal mortality, hypoglycemia and hyperglycemia at birth, and major congenital anomalies. The main study population included all children born between 1996 and 2016 in Finland. The children were divided into four cohorts based on treatment exposure during pregnancy: 1) metformin (only metformin dispensed during pregnancy), 2) combination (both metformin and insulin dispensed), 3) insulin (only insulin dispensed), and 4) naïve (children born to mothers with GDM, but neither metformin nor insulin was dispensed).

The children were followed from their birth until the end of 2016, the occurrence of death, or migration abroad, whichever occurred first. The maximum follow-up for the long-term effects was up to the age of 20 years.

No increased risk was found in the metformin cohort compared to the insulin cohort regarding the risk of developing long-term outcomes: obesity (PS-weighted HR 1.14, 95% confidence interval (CI) 0.83-1.55), hypoglycemia (PS-weighted HR 1.00, 95% CI 0.61-1.64), hyperglycemia (PS-weighted HR 1.23, 95% CI 0.63-2.42), diabetes mellitus (PS-weighted HR 1.19, 95% CI 0.51 - 2.82), and diagnoses related to challenges in motor-social development (PS-weighted HR 1.09, 95% CI 0.93-1.27). Combination treatment was not associated with significantly increased risk of obesity (PS-weighted HR 1.09, 95% CI 0.76-1.58), hypoglycaemia (PS-weighted HR 1.14, 95% CI 0.71-1.83), hyperglycemia (PS-weighted HR 0.22, 95% CI 0.05-1.01), diabetes (PS-weighted HR 0.14, 95% CI 0.02-1.15), or challenges in motor-social development (PS-weighted HR 1.11, 95% CI 0.77-1.59). The low number of hypertension and PCOS diagnoses hindered performing

comparative analyses for these outcomes, and the number of children developing diabetes mellitus was also low. The results were by large consistent when the combination cohort was compared to the insulin cohort.

In an additional analysis, no difference was found for the risk of LGA in the metformin cohort compared to the naïve cohort, as the unadjusted, adjusted, and PS-weighted ORs did not reach statistical significance (unadjusted OR 0.97, 95% CI 0.82, 1.14; adjusted OR 0.97, 95% CI 0.81, 1.17; PS-weighted OR 0.91, 95% CI 0.75, 1.11). In the GDM-only subpopulation there was no difference in the adjusted and unadjusted results, however the risk of being LGA was lower in the metformin cohort compared to the naïve cohort in the PS-weighted model (PS-weighted OR 0.72, 95% CI 0.56, 0.92). For the outcome of SGA, there was no difference found in the metformin cohort compared to the naïve cohort in the unadjusted, adjusted, or PS-weighted results, and the PS-weighted ORs were close to 1 in both the main study population and the GDM-only subpopulation (0.97, 95% CI 0.73, 1.27 and 1.01, 95% CI 0.75, 1.37, respectively).

In summary, based on CLUE, metformin has no increased risk of LGA or SGA birth compared to patients managed without drug intervention. Metformin is superior to insulin in preventing LGA. The lower risk of LGA for metformin versus no treatment may be related to a higher occurrence of (uncontrolled) hyperglycemia in the drug-naïve cohort, leading to fetal hyperinsulinemia and LGA birth.

The results of the registry CLUE were complemented with the published meta-analyses, clinical studies and other registries:

For treatment of PCOS and GDM during pregnancy, hyperglycemia was associated with a higher weight of the offspring in childhood for the long-term follow-up. These results are based on the landmark studies by Vanky (2010) and one study site of Rowan (2008), respectively, but there are also indications in smaller studies by Xu (2019) and Anwar (2019), respectively.

This finding, however, is based on a paucity of data and divergent findings exist (Feig, 2020): The other study site of Rowan (2018) did not see a difference. Paul (2020) also assessed offspring born to mother with GDM and exposed to glibenclamide or metformin in utero at the average age of 9.6 years. There were no significant differences in anthropometrics, glycemic status or diabetes/prediabetes occurrence, the only was on triglyceride (0.75 [0.6,1.0] mmol/l vs. 0.88 [0.7,1.3] mmol/l, p=0.030).In CLUE, metformin alone demonstrated a significantly higher risk compared to insulin for being small for gestational age. Feig (2020) have speculated that the increased number of small infants potentially being related to effects of metformin on mothers leading to reduced food intake, which could then affect weight gain, glycemic control, and nutrient supply (Coll, 2020) , although this did not become evident in the long term weight outcome in CLUE.

Therefore, in case of potential fetal malnutrition (e.g. maternal fasting/undernutrition, insufficient maternal/fetal weight gain or placental problems), metformin should be used with caution to counter the risk of the baby being born small for gestational age.

In CLUE no increased risk of motor-social development changes was found after in utero exposure to metformin. The largest investigation so far with a robust methodology, the case-control study

by Landi (2019) did not find a difference for metformin vs insulin (gestational diabetes) at the age of 4 years. Long-term follow-up of offspring from the largest randomized clinical trial (RCT) did not find a difference for metformin versus insulin (for gestational diabetes) at the age of 18 months to 7.7 years. However, especially the RCT follow-ups are rather small in size.

In summary, there is limited and conflicting evidence for the effect of metformin on the long-term weight outcome of children exposed to metformin in utero, and subsequently uncertainty on the risk of long-term metabolic complications during the offspring life. Furthermore, there is limited evidence available on long term outcomes regarding to motor-social development after the age of 4 years.

Module SVIII Summary of the Safety Concerns

Table 6 Summary of safety concerns

Summary of safety concerns	

Important identified risks	• Lactic acidosis including
	  • Use in patients with renal dysfunction with GFR < 45 ml/min
	  • Concomitant use of iodinated contrast media

Important potential risks	• None
Missing information	• Long-term offspring outcomes after exposure to metformin in utero

Part III: Pharmacovigilance Plan (including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the important identified risk lactic acidosis including use in patients with renal dysfunction with GFR < 45 ml/min and concomitant use of iodinated contrast media:

A specific questionnaire is used in addition to the standard collection form in order 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. Results of these questionnaires will be submitted and discussed in the next subsequent PSURs of the product.

The following points are included in the questionnaire:

- metabolic acidosis: lactate level, blood pH (arterial our 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

The targeted questionnaire is attached in Annex 4.

Other forms of routine pharmacovigilance activities for the important identified risk lactic acidosis including use in patients with renal dysfunction with GFR < 45 ml/min and concomitant use of iodinated contrast media:

A cumulative analysis of the events of the SMQ lactic acidosis will be provided within the next PSURs of the product, with a special focus on CKD stage 3.

III.2 Additional Pharmacovigilance Activities

Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

Part IV: Plans for Post-Authorization Efficacy Studies

Metformin has been marketed for more than 60 years and its efficacy has been well established. There is no requirement for any additional efficacy studies for the approved indications.

Part V: Risk Minimization Plan (including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Table 7 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Lactic acidosis including • use in patients with renal dysfunction with GFR < 45 ml/min • concomitant use of iodinated contrast media: **(important identified risk)**	Routine risk communication: • SmPC section 4.8: Undesirable effects • PL section 4: Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: • Assessment of renal function regarding correct dosage before initiation of treatment and dose adjustment according to renal function is included in SmPC section 4.2 • Contraindications and interactions regarding risk of lactic acidosis are addressed in SmPC section 4.3, and 4.5 • Risk of acute renal failure (contrast induced nephropathy) during treatment with concomitant iodinated contrast media is addressed in SmPC section 4.4, 4.5., and in PL section 2. • Characterization of lactic acidosis and risk factors in SmPC section 4.4 • Risk factors and symptoms of lactic acidosis and how dosage should be adjusted in renal impaired patients PL sections 2-3. Other routine risk minimization measures beyond the Product Information: • Legal status: Prescription-only medicine
Long-term offspring outcomes after exposure to metformin in utero **(missing information)**	Routine risk communication: • SmPC section 4.6: Fertility, pregnancy and lactation • PL section 2: Pregnancy and breast-feeding Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • Legal status: Prescription-only medicine

V.2 Additional Risk Minimization Measures

Routine risk minimization 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 8 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Lactic acidosis including • use in patients with renal dysfunction with GFR < 45 ml/min • concomitant use of iodinated contrast media: (**important identified risk**)	Routine risk minimization measures: • SmPC section 4.2: Posology and method of administration • SmPC section 4.3: Contraindications • SmPC section 4.4: Special Warnings and precautions for use - signs and symptoms of lactic acidosis including risk factors are provided and when to stop treatment - severe renal impairment as a risk factor for lactic acidosis is mentioned - iodinated contrast media discussed as risk factor for lactic acidosis • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction • PL section 2: What you need to know before you take metformin • PL section 3: How to take metformin • PL section 4: Possible side effects • Legal status: Prescription-only medicine Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A specific targeted questionnaire will be used in addition to standard collection form which will enable identification of lab-value confirmed lactic acidosis cases and check for additional risk factors on (acute) renal impairment as well as other causes of lactic acidosis. • Event is under close monitoring and cumulatively discussed in each periodic report Additional pharmacovigilance activities: None
Long-term offspring outcomes after exposure to metformin in utero **(missing information)**	Routine risk minimization measures: • SmPC section 4.6: Fertility, pregnancy and lactation • PL section 2: Pregnancy and breast-feeding • Legal status: Prescription-only medicine Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the Risk Management Plan for Glucophage® and Glucophage® XR and Stagid® (metformin hydrochloride, metformin embonate)

This is a summary of the risk management plan (RMP) for Glucophage®/Glucophage® XR and Stagid®. The RMP details important risks of Glucophage®/Glucophage® XR and Stagid®, how these risks can be minimized, and how more information will be obtained about Glucophage®/Glucophage® XR and Stagid® risks and uncertainties (missing information).

Glucophage®/Glucophage® XR and Stagid® summary of product characteristics (SmPC) and their package leaflet give essential information to healthcare professionals and patients on how Glucophage®/Glucophage® XR and Stagid® should be used.

Important new concerns or changes to the current ones will be included in updates of Glucophage®/Glucophage® XR and Stagid® RMP.

I. The Medicine and What it is used for

Glucophage®/Glucophage® XR and Stagid® are authorized for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycemic control (see respective product information for the full indication). Stagid® is also authorized for the treatment of type 1 diabetes mellitus in adults in combination with insulin therapy. Glucophage® XR is nationally authorized in some countries for treatment of the delay or prevention of type 2 diabetes, a condition arising from increased serum glucose level, but still below the threshold for the diagnosis of overt diabetes. Glucophage®/Glucophage® XR may postpone the onset of type 2 diabetes. Glucophage®/Glucophage® XR and Stagid® contain metformin hydrochloride and metformin embonate as the active substance and they are given orally.

Metformin tablets have been used for 60 years to treat diabetes. Metformin works to control the amount of sugar in the bloodstream because in diabetes the body is unable to do that on its own. It is important that other lifestyle measures, such as diet, exercise and weight reduction are also undertaken as well as using metformin.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Glucophage®/Glucophage® XR and Stagid®, together with measures to minimize such risks and the proposed studies for learning more about Glucophage®/Glucophage® XR and Stagid® risks, are outlined below.

The use of Glucophage®/Glucophage® XR and Stagid® requires prescription by a healthcare professional. Patients and healthcare professionals are informed about the risk of the products in warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC.

Information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary.

If important information that may affect the safe use of Glucophage®/Glucophage® XR and Stagid® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Glucophage®/Glucophage® XR and Stagid® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a causal link with the use of Glucophage®/Glucophage® XR and Stagid®.

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).

List of important risks and missing information	

Important identified risks	• Lactic acidosis including
	  • Use in patients with renal dysfunction with GFR< 45 ml/min
	  • Concomitant use of iodinated contrast media

Important potential risks	• None
Missing information	• Long-term offspring outcomes after exposure to metformin in utero

II.B Summary of Important Risks

Lactic acidosis including • **use in patients with renal dysfunction with GFR < 45 ml/min** • **concomitant use of iodinated contrast media**	
Evidence for linking the risk to the medicine	Several sources provide evidence on lactic acidosis, which is a serious condition with a mortality rate of around 25% if not treated promptly (Renda, 2013): Spontaneous case reports from the post-marketing experience; scientific medical literature, such as Bodmer 2008, Mani 2009, Salpeter 2010, and Scarpello 2008 among others. In the large, updated Cochrane meta-analysis on the risk of fatal and nonfatal lactic acidosis (LA) with metformin use in T2DM, Salpeter (2010) pooled data from 347 comparative trials and cohort studies in diabetic patients treated with different hypoglycemic drugs, with 70,490 patient-years of metformin use and 55,451 patients-years in the non-metformin group, not a single case of lactic acidosis was found. In a large, nested, case-control analysis of the UK general practice research database (Bodmer, 2008), the crude incidence of lactic acidosis was even lower at 3.3 cases per 100,000 person-years among metformin users (with different stages of renal impairment). Relevant co-morbidities known as risk factors for lactic acidosis could be identified in all case subjects (Mani, 2009).
Risk factors and risk groups	Reported cases of lactic acidosis with metformin have occurred primarily in diabetic patients with acute renal failure or prodromal events.

Lactic acidosis including • **use in patients with renal dysfunction with GFR < 45 ml/min** • **concomitant use of iodinated contrast media**	
	The main risk factor for acute renal impairment as indicated by many authors, are diarrhea and vomiting (Rhee, 2017; Bell, 2017). In addition, risk factors include alcohol intake, especially in higher amounts, contrast-induced nephropathy (see below) and drugs / drug classes associated with acute renal impairment (Pazhayattil, 2014; McWilliam, 2007; Markowitz, 2005) such as antihypertensive therapy (including ACE inhibitor, angiotensin II receptor blocker), diuretics, NSAID (including paracetamol), antibiotics, antiviral, antifungal, oncologic drugs, radiocontrast, calcineurin inhibitors, lithium, H2-blocker, statins, gout medication and SGLT2-inhibitors. Further risk factors are poorly controlled diabetes, ketosis, prolonged fasting, severe infection, hepatic insufficiency, dehydration (i.e. severe diarrhea or vomiting) and any conditions associated with hypoxia (such as acute heart failure, acute myocardial infarction) (Lalau, 2010). As mentioned above one of the main risk factors for lactic acidosis is the intravascular administration of iodinated contrast materials in radiologic studies which can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Therefore, depending on the renal function, metformin must be discontinued 48 hours before the test or from the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.
Risk minimization measures	Routine risk minimization measures SmPC section 4.2: Posology and method of administration SmPC section 4.3: Contraindications SmPC section 4.4: Special Warnings and precautions for use– signs and symptoms of lactic acidosis including risk factors are provided SmPC section 4.5: Interaction with other medicinal products and other forms of interaction PL section 2: What you need to know before you take metformin PL section 3: How to take metformin PL section 4: Possible side effects Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine Additional risk minimization measures None
Long-term offspring outcomes after exposure to metformin in utero (missing information)	
Risk minimization measures	Routine risk minimization measures Legal status: Prescription-only medicine

II.C Post-authorization Development Plan

Not applicable.

II.C.1 Studies which are Conditions of the Marketing Authorization

Not applicable.

II.C.2 Other Studies in the Post-authorization Development Plan

Not applicable.

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Part VII Annexes

Annex 1 EudraVigilance Interface (available in electronic format only)

Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme (Not applicable)

Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan (Not applicable)

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV (Not applicable)

Annex 6 Details of Proposed Additional Risk Minimization Activities (Not applicable)

Annex 7a Other Supporting Data (including Referenced Material) (see References)

Annex 7b List of countries where the indication of "reduction of risk or delay of type 2 diabetes" concerning the XR form of metformin hydrochloride is approved.

Annex 8 Summary of Changes to the Risk Management Plan over Time

ELECTRONIC SIGNATURES

Document: RMP Metformin hydrochloride embonate (Glucophage, Stagid), Version 8.1, DLP 01 Oct 2020 - Report

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Business Approval	PPD
PPD	Task Completed (Approval eSign): Approved	Business Approval	PPD
PPD	Task Completed (Approval eSign): Approved	Business Approval	PPD

[1]Targeted questionnaire

Lactic acidosis

(Skip all questions below for which the information are already provided at SAE form or by other mean)

Patient Initials: Birth date: __ __ ____ (dd - mmm - yyyy)

Metformin Daily dose: Date / / (dd/mmm/yyyy)
Time / (hh:mm)
Value of the last dose: (mg)

Clinical presentation / investigations	Details (If yes, please provide lab values and units)
Lactate level	Date and time 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / Unit mg/dl or mmol/l
Metformin plasma level	Date and time 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / Unit mg/l

[1] This form has to be used as addition to SAE collection form. For all AE of special interest following information has to be provided on SAE collection form: [redacted] tcome of AE, Latency period from first and last administration of suspected product prior to AE onset, age, [redacted]/rechallange information.

Metformin concentration in erythrocytes	<u>Date and time</u> 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / <u>Unit</u> mg/l
Blood pH	<u>Date and time</u> 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / ☐ arterial or ☐ venous
Anion gap	<u>Date and time</u> 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / <u>Unit</u> mmol/l

Creatinine before the event	Date and time 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / Unit mg/dl or µmol/l
Creatinine during the event	Date and time 4) (dd/mmm/yyyy) / / (hh:mm) / 5) (dd/mmm/yyyy) / / (hh:mm) / 6) (dd/mmm/yyyy) / / (hh:mm) / Unit mg/dl or µmol/l
Creatinine clearance before the event	Date and time 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / Unit ml/min

Creatinine clearance during the event	<u>Date and time</u> 4) (dd/mmm/yyyy) / / (hh:mm) / 5) (dd/mmm/yyyy) / / (hh:mm) / 6) (dd/mmm/yyyy) / / (hh:mm) / <u>Unit</u> ml/min
Ketonuria	<u>Date and time</u> 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / <u>Unit</u> mg/dl or mmol/l
ß-Hydroxybutyrate	<u>Date and time</u> 1) (dd/mmm/yyyy) / / (hh:mm) / 2) (dd/mmm/yyyy) / / (hh:mm) / 3) (dd/mmm/yyyy) / / (hh:mm) / <u>Unit</u> mmol/l

Risk factors / Differential diagnosis / Alternative etiology	Details (If yes, please provide details, dates, therapy, outcome)
Alcohol consumption	☐ Yes ☐ No ☐ Unknown If yes, please specify
Exposure to contrast media	☐ Yes ☐ No ☐ Unknown If yes, please specify
Infection/sepsis	☐ Yes ☐ No ☐ Unknown If yes, please specify
Renal disorder	☐ Yes ☐ No ☐ Unknown If yes, please specify
Dehydration	☐ Yes ☐ No ☐ Unknown If yes, please specify
Diarrhea	☐ Yes ☐ No ☐ Unknown If yes, please specify
Vomiting	☐ Yes ☐ No ☐ Unknown If yes, please specify
Acute heart failure	☐ Yes ☐ No ☐ Unknown If yes, please specify
Acute myocardial infarction	☐ Yes ☐ No ☐ Unknown If yes, please specify
Other conditions with hypoxia	☐ Yes ☐ No ☐ Unknown If yes, please specify

Concomitant medications (e.g., diuretics, beta-blockers, ACE inhibitors, NSAIDs, HIV therapy, cytostatic chemotherapy, H2-blocker)	☐ Yes ☐ No ☐ Unknown If yes, please specify drug, indication, dose, route, date and duration for each concomitant medication

Signature: _____ Date:_____

Annex 7b List of EU countries where Prediabetes indication is approved

Country	Drug Product	Strength
Bulgaria	Glucophage® XR	500/750/1000
Croatia	Glucophage® XR	500/750/1000
Cyprus	Glucophage® XR	500/750/1000
Hungary	Glucophage® XR	500/750/1000
Latvia	Glucophage® XR	500/1000
Poland	Glucophage® XR	500/750/1000
United Kingdom	Glucophage® XR	500/750/1000

Annex 8 Summary of Changes to the Risk Management Plan over Time

Table 1 refers to the "Summary of changes to the Risk Management Plan over time" according to the EMA Guidance on format of the risk management plan (RMP) in the EU – in integrated format (EMA/465932/2013 Rev.1; 25 July 2013)

Version	Date	Safety concerns	Comment
1.0	07 September 2007	**Important Identified Risks** • Lactic acidosis **Important Potential Risk** None **Missing Information** None	
2.0	16 February 2010	**Important Identified Risks** • Lactic acidosis Gastrointestinal disorders such as nausea, vomiting, • Skin reactions such as erythema, pruritus, or urticaria • Taste disturbance • Decrease of vitamin B12 absorption • Liver function tests abnormalities or hepatitis **Important Potential Risk** None **Missing Information** None	
3.0	05 December 2013	**Important Identified Risk** • Lactic acidosis with and without renal failure **Important Potential Risks** • Leukocytoclastic vasculitis **Missing Information** None	The important identified risk of lactic acidosis has been amended to consider lactic acidosis in the presence and absence of renal failure. Skin reactions, gastrointestinal disturbances, taste disturbance and liver function test abnormalities have been removed as Important Identified Risks as with the current experience of metformin there is no evidence that these events meet the definition of "Important" Identified Risks (as defined in Module V of Good Pharmacovigilance Practice) taking into account the impact on the individual, the seriousness of the risk and the impact on public health.

Version	Date	Safety concerns	Comment
3.1	17January 2014	**Important Identified Risk** • Lactic acidosis with and without renal failure **Important Potential Risks** • Leukocytoclastic vasculitis **Missing Information** • None	Version 3.0 only covered metformin hydrochloride. However, all data provided in RMP 3.0 such as patient exposure also referred to metformin embonate. Therefore, metformin embonate was added in version 3.1.
4.0	14 August 2014	**Important Identified Risk** • Lactic acidosis with and without renal failure **Important Potential Risk** • Leukocytoclastic vasculitis **Missing Information** • None	Risk minimization measures included (outer box warning)
5.0	22 December 2016	**Important Identified Risks** • Lactic acidosis with and without renal failure • Use in patients with renal dysfunction with GFR < 30 ml/min • Concomitant use of iodinated contrast media **Important Potential Risks** • Leukocytoclastic vasculitis • Off-label use (especially in female patients with PCOS) **Missing information** • Use in children younger than 10 years • Use in pregnancy and lactation	As an outcome of the PRAC assessment report (PSUSA/00002001/201504) and the Referral under article 31 of Directive 2001/83/EC procedure RMP was updated and discrepancies between the different presented RMP from other companys aligned. Annex 7 included (targeted follow-up questionnaire)
5.1	07 April 2017	**Important Identified Risks** • Lactic acidosis with and without renal failure • Use in patients with renal dysfunction with GFR < 30 ml/min • Concomitant use of iodinated contrast media **Important Potential Risks** • Leukocytoclastic vasculitis • Off-label use (especially in female patients with PCOS) **Missing information** • Use in children younger than 10 years Use in pregnancy and lactation	As requested in Type Ib variation updated preliminary variation assessment report for Glucophage (FR/H/181/001-003/IB/121) dated 18 March 2017, a minor change in the section “safety-issue 3“ of the table “detailed description of action taken in the PARTII: Module SV – Post-authorization Experience” was done as the PRAC requested only the **MAH for the innovator product Glucophage** to provide information. Annex 7 Targeted follow-up questionnaire was also modified as per PVAR.
6.0	02 June 2017	**Important Identified Risks** • Lactic acidosis with and without renal failure • Use in patients with renal dysfunction with GFR < 30 ml/min • Concomitant use of iodinated contrast media	Annex 7 Targeted follow-up questionnaire was modified and one point regarding “metformin daily dose and date/time/value of the last dose” added

Version	Date	Safety concerns	Comment
		Important Potential Risks • Leukocytoclastic vasculitis • Off-label use (especially in female patients with PCOS) **Missing information** • Use in children younger than 10 years Use in pregnancy and lactation	

Table 2 refers to the "Summary of changes to the Risk Management Plan over time" according to the EMA Guidance on format of the risk management plan (RMP) in the EU – in integrated format (EMA/PRAC/613102/2015 Rev.2; 30 March 2017)

Version	Approval date Procedure	Change
7.0		Adaption to new EU GVP template Safety concerns Rearranging of safety concerns to one important identified risk and change of risk use in patients with renal dysfunction with GFR <30 ml/min to GFR < 45 ml/min **Important Identified Risks** Lactic acidosis • Use in patients with renal dysfunction with GFR < 45 ml/min • Concomitant use of iodinated contrast media **Important Potential Risks** • Leukocytoclastic vasculitis • Off-label use in female patients with PCOS Added: Cognitive impairment due to vitamin B12 deficiency **Missing information** • Use in children younger than 10 years • Use in pregnancy and lactation
7.1		-Addition of countries for prediabetes indication as per Annex 7b (with reference in the Product Overview Section). -Removal of the following important potential risks with rationale: • 'Leukocytoclastic vasculitis' • 'Cognitive impairment due to vitamin B12 deficiency' • 'Off-label use in female patients with PCOS' -Removal of 'Use in children younger than 10 years' from the section "Missing information", with rationale. -Addition of 'Initiation of treatment in patients above 75 years for the reduction of risk or delay of type 2 diabetes' to the section "Missing information".
7.2	10 March 2020	Removal of 'Initiation of treatment in patients above 75 years for the reduction of risk or delay of type 2 diabetes' from the section "Missing information".
7.3	12 May 2020 (internal approval date)	Addition of new strength Glucophage® XR 850 mg to Part I: Product Overview

Version	Approval date Procedure	Change
8.0		Update of the Missing information: Pregnancy and lactation revised to: Long-term offspring outcomes after exposure to metformin in utero Addition of new strength Glucophage® XR 850 mg to Part I: Product Overview (was already introduced in version 7.3 but again highlighted in this version)
8.1		Update of the Missing information: pregnancy and lactation revised to: Long-term offspring outcomes after exposure to metformin in utero • Rationale provided why 'lactation' has been removed • Incidence of hyperglycemia in pregnancy and periconceptional phase provided • Information on treatment of hyperglycemia during pregnancy provided • Results from additional analysis of PASS CLUE added RMP harmonized with Guidance on the format of RMP in the EU