Module 1.8.2 – Risk Management Plan – Metformin

EU Risk Management Plan for:	Metformin
RMP version to be assessed as part of this application: RMP Version number:	0.3
Data lock point for this RMP:	20 Mar 2019
Date of final sign off:	2p1 Jan 2020
Rationale for submitting an updated RMP:	New application for Metformin Hydrochloride Brown & Burk 500 mg prolonged-release Tablets Metformin Hydrochloride Brown & Burk 750 mg prolonged-release Tablets Metformin Hydrochloride Brown & Burk 1000 mg prolonged-release Tablets
Summary of significant changes in this RMP:	Query response
Other RMP versions under evaluation • RMP version number • Submitted on • Procedure number	 Not applicable Not applicable Not applicable
Details of the currently approved RMP • Version number • Approved with procedure • Date of approval (Opinion date)	Not applicable
QPPV name:	[redacted]
QPPV signature:	[redacted]

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Part I: Product(s) Overview

Active substance (s) (INN or common name):	Metformin Hydrochloride
Pharmacotherapeutic group (s): (ATC Code):	Pharmacotherapeutic group: Oral hypoglycaemic agents ATC code: A10BA02
Marketing Authorisation Holder or Applicant:	Brown & Burk UK Limited [redacted]
Medicinal products to which this RMP refers	3
Invented name (s) in the European Economic Area (EEA)	Metformin hydrochloride Brown & Burk 500 mg prolonged-release Tablets Metformin hydrochloride Brown & Burk 750 mg prolonged-release Tablets Metformin hydrochloride Brown & Burk 1000 mg prolonged-release Tablets
Marketing authorisation procedure	National
Brief description of the product	Chemical Class: The chemical classification of metformin is Biguanides ATC code: A10BA02
	Summary of mode of action: Metformin is a biguanide with anti hyperglycaemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

	Metformin may act via 3 mechanisms: 1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis. 2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation. 3. And delay of intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date. In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin reduces total cholesterol, LDL, cholesterol and triglycerides levels.
	Important information about its composition: Not Applicable
Hyperlink to the Product Information	Please see Module 1.3.1 of the current eCTD sequence
Indication (s) in the EEA	Current (if applicable): Metformin Hydrochloride Brown & Burk [500/750/1000] mg prolonged-release Tablets • Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adults, overweight patients with IGT* and/or IFG*, and/or increased HbA1C who are: – At high risk for developing overt type 2 diabetes mellitus and – Still progressing towards type 2 diabetes despite implementation of intensive lifestyle change for 3 to 6 months *IGT: Impaired Glucose Tolerance *IFG: Impaired Fasting Glucose Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin prolonged release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): **Metformin Hydrochloride Brown & Burk [500/750/1000] mg prolonged-release Tablets** **Adults with normal renal function (GFR≥90 mL/min):** *Reduction in the risk or delay of the onset of the type 2 diabetes* • Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control. • The therapy should be initiated with one tablet Metformin Hydrochloride prolonged release tablets 500mg once daily with the evening meals. • After 10 to 15 days the dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1C values to be within the normal range). A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 4 tablets (2000 mg) once daily with the evening meal • It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued. • A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible. *Monotherapy in Type 2 diabetes mellitus and combination with other oral antidiabetic agents:* • The usual starting dose is one tablet of Metformin prolonged release 500 mg once daily. • After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.

	• In patients already treated with Metformin Tablets, the starting dose of metformin hydrochloride prolonged release should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin hydrochloride at a dose above 2000 mg daily, switching to Metformin Hydrochloride prolonged release is not recommended. • Dosage increases should be made in increments of 500 mg every 10- 15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not achieved on once daily dosing of Metformin Hydrochloride prolonged release at a maximum dose of 2000 mg a day, then a twice daily dosing schedule should be considered with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum dose of 3000 mg daily. • If transfer from another oral anti-diabetic is intended, discontinue the other agent and initiate metformin at the dose indicated above. • Metformin Hydrochloride prolonged release tablets 750 mg and Metformin Hydrochloride prolonged release tablets 1000 mg are intended for patients who are already treated with Metformin tablets (prolonged or immediate release). • The dose of Metformin Hydrochloride prolonged release 750 mg or Metformin Hydrochloride prolonged tablets 1000 mg should be equivalent to the daily dose of Metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal. *Combination with insulin:* Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Metformin prolonged release is 500 mg once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. For patients already treated with metformin and insulin in combination therapy, the dose of

	Metformin Hydrochloride prolonged release tablets 750 mg or Metformin Hydrochloride prolonged release tablets 1000 mg should be equivalent to the daily dose of Metformin tablets up to maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.
	Proposed (if applicable): Not applicable
Pharmaceutical form (s) and strengths	Current (if applicable): Prolonged release tablets, 500/750/1000 mg
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU	Yes ☐ No ☑

Part II: Safety Specification

The marketing authorisation application (MAA) for Metformin Hydrochloride Brown & Burk [500/750/1000] mg prolonged release Tablets is being submitted under Article 10 (1) of Directive 2001/83/EC.

In accordance with section V.C.1.1 Table V.5 of the Guidelines on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (EMA/838713/2011, Rev 2), Part II: Modules SI to SVII of this RMP are omitted.

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns*	
Important identified risk	Lactic acidosis (occurring with or without renal failure/impairment and/or concomitant use with iodinated contrast media)
Important potential risks	Leukocytoclastic vasculitis
Missing information	Use during pregnancy and lactation

Part III: Pharmacovigilance Plan (Including post-authorisation safety studies)

III.1 Routine Pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires

Following the Referral procedure under Article 31 (EMEA/H/A-31/1432) of Directive 2001/83/EC which issued a final legally binding decision (12 December 2016) by the European Commission (EC), a targeted questionnaire will be implemented 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. The lactic acidosis targeted follow up questionnaire is provided in Annex 4 of the RMP.

III.2 Additional Pharmacovigilance activities

No additional risk management activities are required. So no post authorisation safety studies or additional pharmacovigilance activities are planned for this product.

III.3 Summary table of additional Pharmacovigilance activities

Not Applicable

Part IV: Plans for post-authorisation efficacy studies

In line with section V.C.1.1 Table V.5 of the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (EMA/838713/2011 Rev 2), Part IV of this RMP is omitted. No additional post-authorisation efficacy studies are currently required.

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

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product. Hence, the following sections V.1, V.2 and V.3 are not applicable.

V.1 Routine Risk minimisation measures

In line with the reference product, routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

V.2 Additional Risk Minimisation Measures

Not Applicable

V.3 Summary table of risk minimisation measures

Not Applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Metformin Hydrochloride Brown & Burk [500, 750 and 1000] mg prolonged release Tablets (metformin hydrochloride)

This is a summary of the risk management plan (RMP) for Metformin Hydrochloride Brown & Burk [500, 750and 1000] mg prolonged release Tablets (hereinafter referred to as Metformin). The RMP details important risks of Metformin, how these risks can be minimised and how more information will be obtained about Metformin's risks and uncertainties (missing information).

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

Important new concerns or changes to the current ones will be included in updates of Metformin's RMP.

I. The medicine and what it is used for

Metformin is authorised for treatment of Type 2 diabetes when diet and exercise changes alone have not been enough to control blood glucose (sugar) and used together with diet and exercise to lower the risk of developing Type 2 diabetes in overweight adults, when diet and exercise alone for 3 to 6 months have not been enough to control blood glucose (see SmPC for the full indication). It contains metformin hydrochloride as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Metformin, together with measures to minimise such risks and the proposed studies for learning more about Metformin risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging ;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

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

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

II.A List of important risks and missing information

Important risks of Metformin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Metformin. 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).

Summary of safety concerns	
Important identified risk	Lactic acidosis (occurring with or without renal failure/impairment and/or concomitant use with iodinated contrast media)
Important potential risks	Leukocytoclastic vasculitis
Missing information	Use during pregnancy and lactation

II.B Summary of important risks

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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 other studies in post-authorisation development plan

There are no studies required for Metformin.

Part VII. Annexes

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Annex 1- EudraVigilance Interface

Not applicable

Annex 2- Tabulated summary of planned, ongoing and completed pharmacovigilance study programme

Not applicable

Annex 3- Protocols for proposed, on-going and completed studied in the pharmacovigilance plan

Not applicable

Annex 4- Specific adverse drug reaction follow-up form

Targeted Questionnaire Form

Metformin - Targeted Questionnaire Follow-up Form

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Log/AER No: _____ **Date** _____

I. Patient Details

Patient Initials: _____ DOB/Age: _____ / ☐ Years, WEIGHT: _____Kg

Sex: ☐ Female ☐ Male

II. Product Details

Suspected Drug(s) ***(Please specify Brand Names and Batch Nos. if known)***	**Daily Dosage**	**Dose, time and Value of last dose**	**Frequency**	**Date Started**	**Date stopped**	**Indication(s) for using the drug**
1. **Metformin**						
2.						
3						
Concomitant Drug(s) including self-medication taken on the same and/or 3 months before						
1.						
2.						
3						

Other Information e.g. medical history, allergies, pregnancy, smoking, alcohol use, please enclose any relevant laboratory results

_____

_____

_____

_____

III. Investigations / Laboratory details

Investigation / lab test name	**Test #1 Date performed**	**Result**	**Units**	**Test #2 Date performed**	**Result**	**Units**	**Reference range**
1. Metabolic acidosis							
a. Lactate level							
b. Blood pH (arterial our venous)							
c. Anion gap							
d. Ketonuria							
e. β-hydroxybutyrate							
Comments, if any							
2. Metformin plasma level							

Investigation / lab test name	Test #1 Date performed	Result	Units	Test #2 Date performed	Result	Units	Reference range
3. Metformin concentration in erythrocytes							
Comments, if any							

III. Information on Renal Function Test (RFT)

Renal Function test	Test #1 Date performed	Result	Units	Test #2 Date performed	Result	Units	Reference range
Known values before the event							
Albumin to Creatinine Ratio (ACR)							
Glomerular Filtration Rate (GFR)							
Serum creatinine test							
Blood urea nitrogen (BUN)							
Comments, if any							
Values during the event							
Albumin to Creatinine Ratio (ACR)							
Glomerular Filtration Rate (GFR)							
Serum creatinine test							
Blood urea nitrogen (BUN)							
Comments, if any							

Renal Function test	Test #1 Date performed	Result	Units	Test #2 Date performed	Result	Units	Reference range

Discuss regarding any of the below risk factors and provide details of each risk factor as mentioned in below table if applicable:

Risk Factors/ Medical History	Event Status	Start date if available
Alcohol use	☐ Past, ☐Current ☐ Never If past/current, please fill the AUDIT test below	
Comments:		
Exposure to contrast media	☐ Past, ☐on-going ☐ Not experienced If past/on-going, provide the names	
Comments:		
Infection/sepsis	☐ Past, ☐on-going ☐ Not experienced	
Comments:		
Renal disease	☐ Past, ☐on-going ☐ Not experienced	
Comments:		
Dehydration, Diarrhoea, Vomiting	☐ Past, ☐on-going ☐ Not experienced	
Comments:		
Acute heart failure	☐ Past, ☐on-going ☐ Not experienced	
Comments:		
Acute myocardial infarction	☐ Past, ☐on-going ☐ Not experienced	
Comments:		
other conditions with	☐ Past, ☐on-going ☐ Not experienced	

Risk Factors/ Medical History	Event Status	Start date if available
hypoxia		
Comments:		

Alcohol Use Disorders Identification Test (AUDIT):

Questions	Scoring system*					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times per month	2 to 3 times per week	4 times or more per week	
How many units of alcohol do you drink on a typical day when you are drinking?	0 to 2	3 to 4	5 to 6	7 to 9	10 or more	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No	-	Yes, but not in the last year	-	Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No	-	Yes, but not in the last year	-	Yes, during the last year	
Total AUDIT Score						

Metformin - Targeted Questionnaire Follow-up Form

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***Scoring System:**
- 0 to 7 indicates low risk
- 8 to 15 indicates increasing risk
- 16 to 19 indicates higher risk,
- 20 or more indicates possible dependence

Reporter's Name:

Signature:

Date:

Annex 5- Protocols for proposed and on-going studies in RMP part IV

Not applicable

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

Not applicable

Annex 7- Other supporting data (including referenced material)

Not applicable

Annex 8- Summary of changes to the risk management plan over time

Not applicable