EU Risk Management Plan for Glyxambi (empagliflozin + linagliptin)

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Rationale for submitting an updated RMP:	Revision of safety concerns in line with the linagliptin mono component.
Summary of significant changes in this RMP:	*Safety concerns* Removal of important identified risk 'Pancreatitis' and important potential risk 'Pancreatic cancer' (in line with the linagliptin mono component) Module SVIII; Parts III and VI; Appendices 4, 7, and 8)
Other RMP versions under evaluation:	Not applicable.
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QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substances (INN or common name)	Empagliflozin/linagliptin FDC
Pharmacotherapeutic group (ATC code)	A10BD19 (empagliflozin: SGLT-2 inhibitor, linagliptin: DPP-4 inhibitor)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	1
Invented name in the EEA	Glyxambi
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Empagliflozin: SGLT-2 inhibitor Linagliptin: DPP-4 inhibitor
	Summary of mode of action *Empagliflozin* Empagliflozin is a selective inhibitor of SGLT-2. SGLT-2 is expressed in the renal proximal tubes and transports glucose across the membrane against a concentration gradient, accounting for about 90% of the total renal glucose re-absorption. Inhibition of SGLT-2 decreases the renal re-absorption of glucose, thereby increasing urinary glucose excretion and lowering plasma glucose levels. In addition, the calorie loss associated with the increased glucose excretion may result in weight loss. Further, SGLT-2 inhibitors may reduce blood pressure, possibly via a mild diuretic effect. *Linagliptin* Linagliptin is a selective and reversible DPP-4 inhibitor. Inhibition of DPP-4 raises the level of incretin hormones (most importantly GLP-1), which are usually degraded rapidly by the enzyme. GLP-1 is secreted by the gut in response to a food stimulus and it stimulates insulin secretion by β-cells of the pancreas. Inhibiting DPP-4 therefore results in elevated GLP-1 levels with a more pronounced insulin secretion in response to food and thus improved glycaemic control in patients with T2DM.

PI.Table 1 (cont'd) Product Overview

	Important information about its composition Not applicable
Hyperlink to the Product Information	Product information
Indication in the EEA	*Current* Glyxambi, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus • to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Glyxambi do not provide adequate glycaemic control • when already being treated with the free combination of empagliflozin and linagliptin
	Proposed Not applicable
Dosages in the EEA	*Current* Once daily, oral. The recommended starting dose is 1 film-coated tablet of Glyxambi 10 mg/5 mg (10 mg empagliflozin plus 5 mg linagliptin)
	Proposed Not applicable
Pharmaceutical form and strengths	*Current* Film-coated tablet, empagliflozin/linagliptin 10 mg/5 mg, 25 mg/5 mg
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
DPP-4	Dipeptidyl peptidase-4
EEA	European Economic Area
EU	European Union
FDC	Fixed-dose combination
GLP-1	Glucagon-like peptide 1
INN	International Non-proprietary Name
RMP	Risk Management Plan
SGLT-2	Sodium-dependent glucose co-transporter 2
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Glyxambi is a fixed combination product with no new active substance. In line with GVP Module V Revision 2, this module is not applicable.

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

The empagliflozin/linagliptin FDC was investigated in a non-clinical safety programme compliant with the "Guidance for Industry: non-clinical safety evaluation of drug or biologic combinations" Food and Drug Administration, Center for Drug Evaluation and Research 2006 [R12-5450] and the "Guideline on the non-clinical development of fixed combinations of medicinal products" EMEA 2008 [R11-2414]. The pattern of clinical signs, clinical pathology changes, and morphological alterations observed in animals exposed up to toxic dose levels of the FDC is consistent with that observed for empagliflozin and linagliptin when given individually. The spectrum of changes was slight to minimal; the changes were in most cases fully reversible. Neither a synergistic nor an additive effect with regard to adverse findings was evident in any of these studies. The alterations observed in non-clinical safety studies are considered to be related to the pharmacological activity of empagliflozin and/or linagliptin.

The results of non-clinical toxicology studies are summarised below with the corresponding safety concerns relevant to human usage. No specific non-clinical safety pharmacology and drug-drug interaction studies were performed. No other toxicity-related information or data has been identified.

SII.1.1 Toxicity

The FDC of empagliflozin and linagliptin combines the SGLT-2 inhibitor empagliflozin and the DPP-4 inhibitor linagliptin. Combination toxicity studies in the Wistar rat up to 13 weeks were performed as bridging studies to the complete non-clinical development programmes conducted with empagliflozin and linagliptin. In addition, embryo-foetal development studies in the Wistar rat were performed with the combination.

Core toxicity studies for the combination of empagliflozin and linagliptin
In combination toxicity studies predominantly changes either directly or indirectly related to the exaggerated pharmacodynamic activity of the SGLT-2 inhibitor empagliflozin were seen. In the 13-week combination toxicity study in the rat, the NOAEL of the combined compounds was 100 mg/kg/day empagliflozin and 20 mg/kg/day linagliptin (13 times the clinical AUC exposure for both compounds). In the group given 300 mg/kg/day empagliflozin (54 times the clinical exposure) in combination with 60 mg/kg/day linagliptin (60 times the clinical exposure), adverse findings related to empagliflozin were seen. These results were in line with the data of the respective 13-week mono studies. No adverse combination effects were observed in the 13-week toxicity study in the rat.

Reproductive toxicity studies for the combination of empagliflozin and linagliptin
The combination of empagliflozin and linagliptin was shown to be non-teratogenic up to and including a dose of 700 mg/kg/day empagliflozin (253 times the clinical exposure) and

140 mg/kg/day linagliptin (353 times the clinical exposure) in the embryo-foetal development study in the rat. A NOAEL for the combined compounds of 300 mg/kg/day empagliflozin (99 times the clinical exposure) and 60 mg/kg/day linagliptin (227 times the clinical exposure) was derived for both maternal and embryo-foetal toxicity in this study. Combination effects in pregnant rats were restricted to reduced terminal body weight, which were seen at the high dose of 700 mg/kg/day empagliflozin combined with 140 mg/kg/day linagliptin.

Relevance to human usage
The performed combination studies showing no adverse combination effects indicate no combination effects of human relevance.

SII.1.2 Safety pharmacology

No other safety pharmacology-related information or data has been identified.

SII.1.3 Other toxicity-related information or data

No other toxicity-related information or data has been identified.

SII.2 REFERENCES

SII.2.1 Published references

R11-2414 European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP): guideline on the non-clinical development of fixed combinations of medicinal products (London, 24 January 2008, doc.ref.EMEA/CHMP/SWP/258498/2005). Website ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003976.pdf (access date: 27 May 2011) 2008.

R12-5450 Guidance for industry: nonclinical safety evaluation of drug or biologic combinations (March 2006, pharmacology and toxicology). Website fda.gov/OHRMS/DOCKETS/98fr/05d-0004-gdl0002.pdf (access date:05 Dec 2012); Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2006.

SII.2.2 Unpublished references

Not applicable.

ABBREVIATIONS

AUC	Area under the curve
DPP-4	Dipeptidyl peptidase 4
EMEA	European Medicines Agency (re-named into EMA since 2009)
FDC	Fixed-dose combination
NOAEL	No observed adverse effect level
SGLT-2	Sodium glucose co-transporter 2

MODULE SIII CLINICAL TRIAL EXPOSURE

An overview of the safety analysis set used for the exposure calculations is given in the following table.

SIII.Table 1 Overview of safety analysis set

SAF	Description	Trials included
SAF-L8	All phase III, randomised, double-blind trials in patients with T2DM	1275-0001, 1275-0009, 1275-0010, 1275-0013, 1275-0019

Trial 1275-0001: treatment-naïve and metformin treated patients; trials 1275-0010 and 1275-0013: 10 mg and 25 mg empagliflozin

Note: as no difference in the efficacy or safety was observed between the low or high dose group, only the combined treatment of Empa/Lina (=Empa 10mg + Lina 5mg FDC or Empa 25mg + Lina 5mg FDC) is displayed for SAF-L8.

The total exposure was 1053.1 PY. About half of the patients (50.6%) were exposed for 52 weeks or longer (this being due to the inclusion of trial 1275-0001 in this pooling). Further detail is given in the following table.

SIII.Table 2 Duration of exposure (SAF-L8) – TS

	Empa/Lina
	Number of patients, N (%)
Cumulative exposure	
≥1 day	1410 (100.0)
≥24 weeks	1296 (91.9)
≥52 weeks	714 (50.6)
Total exposure [PY]	1053.1

Data source: data on file, RU1540, Table 65.3.1.1

Overall more male than female patients participated in the trials. The number of patients was highest in the age category <65 years, with the number of patients declining with increasing age. There were no patients aged 85 years or older. Further detail is given in SIII.Table 3.

The majority of patients were White, followed by Asian, and then Black/African American patients. Further detail is given in SIII.Table 4.

SIII.Table 3 Age group and gender (SAF-L8) - TS

	Empa/Lina	
Gender/age group [years]	**Number of patients, N**	**Person-time [PY]**
Male		
<65	678	502.6
65 to <75	171	137.5
75 to <85	30	26.3
Female		
<65	419	304.9
65 to <75	100	73.9
75 to <85	12	7.9

Data source: data on file, RU1540, Table 65.3.1.4

SIII.Table 4 Ethnic origin (SAF-L8) - TS

	Empa/Lina	
Race	**Number of patients, N**	**Person-time [PY]**
White	774	546.6
Asian	527	427.7
Black/African American	68	46.5
American Indian/Alaska Native	38	30.4
Hawaiian/Pacific Islander	3	1.9

Data source: data on file, RU1540, Table 65.3.1.5

SIII.1 REFERENCES

Not applicable.

ABBREVIATIONS

Empa	Empagliflozin
FDC	Fixed dose combination
Lina	Linagliptin
PY	Patient year
SAF	Safety analysis set
T2DM	Type 2 diabetes mellitus
TS	Treated set

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Glyxambi is a fixed combination product with no new active substance. In line with GVP Module V Revision 2, this module is not applicable.

MODULE SV POST-AUTHORISATION EXPERIENCE

Glyxambi is a fixed combination product with no new active substance. In line with GVP Module V Revision 2, this module is not applicable.

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Glyxambi is a fixed combination product with no new active substance. In line with GVP Module V Revision 2, this module is not applicable.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

Glyxambi is a fixed combination product with no new active substance. In line with GVP Module V Revision 2, this module is not applicable.

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

There are no important identified or potential risks or missing information for Glyxambi.

SVIII.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

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

There are no safety concerns for Glyxambi and therefore no associated pharmacovigilance activities other than routine risk minimisation measures.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Glyxambi is a fixed combination product with no new active substance, and there are no planned or ongoing post-authorisation efficacy studies imposed for any of the mono components or for the combination. In line with GVP Module V, Revision 2, this module is not applicable.

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

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

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR GLYXAMBI (EMPAGLIFLOZIN + LINAGLIPTIN)

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

Glyxambi's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Glyxambi should be used.

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

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

I. THE MEDICINE AND WHAT IT IS USED FOR

Glyxambi is authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (see SmPC for the full indication). It contains empagliflozin and linagliptin as the active substances and it is given by oral administration.

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

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

There are no important risks or missing information topics for Glyxambi.

ABBREVIATIONS

EMA	European Medicine Agency
EPAR	European Public Assessment Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART VII APPENDICES

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APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse event follow-up forms for Glyxambi.

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

There are no proposed additional risk minimisation activities for Glyxambi.