Boehringer Ingelheim

EU Risk Management Plan for Synjardy (empagliflozin + metformin)

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RMP version to be assessed as part of this application:

RMP version number:	17.1
Data lock point for this RMP:	17 Apr 2024
Date of final sign off:	16 Oct 2024
Rationale for submitting an updated RMP:	Consolidation of v16.1 (current EMA approved version, consolidation of v15.0 + v16.0) and v17.0 (milestone completion PASS 1245-0097 and removal of important potential risk 'Urinary tract carcinogenicity')
Summary of significant changes in this RMP:	V15.0 *Safety concerns* Removal of important potential risk 'Pancreatitis' *Pharmacovigilance Plan* Removal of pancreatitis questionnaire *Other* Administrative update (Module SVIII; Parts III, VI; Appendices 7, 8) V16.0 *New indication* - Update of the clinical trial exposure tables in Module SIII to include data from the DINAMO trial (1218-0091) - Update of Part VI with the new proposed indication - Update of Appendix 7 to include summary of results from the DINAMO trial (1218-0091) *Pharmacovigilance Plan* Milestone update PASS 1245-0097 (Part III, Appendix 2) *Other* Administrative updates (Part I, Appendix 8)

Summary of significant changes in this RMP (cont'd):	V17.0 *Safety concerns* Removal of important potential risk 'Urinary tract carcinogenicity' (in line with the empagliflozin mono component) *Pharmacovigilance Plan* Milestone completion PASS 1245-0097 (Module SVIII; Parts III, VI; Appendices 2, 3c, 7, 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.

TABLE OF CONTENTS

PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substances (INN or common name)	Empagliflozin/metformin FDC
Pharmacotherapeutic group (ATC code)	A10BD20 (empagliflozin: SGLT-2 inhibitor, metformin: biguanide)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	1
Invented name in the EEA	Synjardy
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Empagliflozin: SGLT-2 inhibitor Metformin: biguanide
	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. *Metformin* Although its mechanism of action is not yet fully understood, metformin lowers blood glucose levels primarily by suppressing hepatic gluconeogenesis. Metformin improves the insulin sensitivity of peripheral tissues, decreases gastrointestinal tract glucose absorption, and acts as an insulin sensitiser without exerting any direct effect on pancreatic beta-cell insulin secretion.

PI.Table 1 (cont'd) Product Overview

Brief description of the product (cont'd)	*Important information about its composition* Not applicable
Hyperlink to the Product Information	Product information
Indication in the EEA	*Current* Synjardy is indicated in adults and children aged 10 years and above for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise: • in patients insufficiently controlled on their maximally tolerated dose of metformin alone • in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products • in patients already being treated with the combination of empagliflozin and metformin as separate tablets. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the population studied, see SmPC sections 4.4, 4.5 and 5.1.
	Proposed Not applicable

PI.Table 1 (cont'd) Product Overview

Dosages in the EEA	*Current* Twice daily, oral
	Proposed Not applicable
Pharmaceutical form and strengths	*Current* Film-coated tablet 5 mg empagliflozin plus 850 mg or 1000 mg metformin hydrochloride 12.5 mg empagliflozin plus 850 mg or 1000 mg metformin hydrochloride
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EU	European Union
FDC	Fixed-dose combination
INN	International Non-proprietary Name
RMP	Risk Management Plan
SGLT-2	Sodium-dependent glucose co-transporter 2
SmPC	Summary of Product Characteristic
T2DM	Type 2 diabetes mellitus

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Synjardy 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

SII.1.1 Toxicity

Combination studies of empagliflozin with metformin were conducted, and consisted of general toxicology studies of up to 13 weeks and embryofoetal development studies in Wistar (Han) rats.

Combination toxicology studies in rats of up to 13 weeks with empagliflozin/metformin did not reveal any additional target organs when compared to empagliflozin or metformin alone. Empagliflozin alone and/or in combination with metformin resulted in expected pharmacologic glucosuric and glucose-lowering effects as seen in previous studies with empagliflozin. Decreases in body weight, electrolyte variances (mainly hypochloraemia), aciduria, liver enzyme elevations (less than 2-fold), and increases in kidney and liver weights were exacerbated when empagliflozin was combined with metformin, however only hypochloraemia at ≥100/≥200 mg/kg/day empagliflozin/metformin and body weight decreases at 200/400 mg/kg/day empagliflozin/metformin were considered adverse. The NOAEL was considered to be 50/100 mg/kg/day empagliflozin/metformin (4x and 2x the clinical exposure for empagliflozin and metformin respectively).

In embryo-foetal development studies in pregnant rats with co-administration of empagliflozin and metformin, there were no teratogenic effects that were attributed to empagliflozin. Skeletal variations were mainly observed at 300/600 mg/kg/day and 0/600 mg/kg/day empagliflozin/metformin and were considered to be signs of a delayed development secondary to maternal toxicity. Malformations occurred almost exclusively in the 0/600 and 300/600 mg/kg/day empagliflozin/metformin dose groups and were considered to be due to metformin and not to empagliflozin (these occurred at 49x and 8x the clinical exposure for empagliflozin and metformin respectively). The NOAEL was 100/200 mg/kg/day empagliflozin/metformin for embryo-foetal development (14-times and 4-times the clinical exposure for empagliflozin and metformin respectively) and 30/60 mg/kg/day for maternal toxicity (4-times and 1-time the exposure as maximum daily dose of empagliflozin and metformin respectively).

SII.1.2 Safety pharmacology

No general safety pharmacology studies have been carried out specifically on empagliflozin/metformin.

SII.1.3 Other toxicity-related information or data

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

SII.2 REFERENCES

Not applicable.

ABBREVIATIONS

NOAEL	No observed adverse effect level

MODULE SIII CLINICAL TRIAL EXPOSURE

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

SIII.Table 1 Overview of safety analysis sets

SAF/trial	Description	Trials included
Trial 1218-0091	Randomised, placebo-controlled clinical trial in paediatric patients (DINAMO)	1218-0091
SAF-C4[1]	Randomised, double-blind, placebo-controlled trials	1245-0019, 1245-0023*(met)*, 1245-0023*(met+SU)*, 1245-0033, 1245-0049, 1275-0009, 1276-0010
Trial 1245-0025[2]	Randomised, double-blind, placebo-controlled trial in T2DM patients with increased cardiovascular risk (EMPRA-REG OUTCOME)	1245-0025
Pooling SAF-C4+1218-0091	Randomised, double-blind, placebo-controlled trials (adult and paediatric T2DM indication)	1245-0019, 1245-0023*(met)*, 1245-0023*(met+SU)*, 1245-0033, 1245-0049, 1275-0009, 1276-0010, 1218-0091

[1] Only patients on metformin background, with or without other antidiabetic background medication, are included. For trials 1245-0033 and 1245-0049, only data from the first 18 weeks, when the background insulin dose was to be stable, were included.

[2] Metformin subgroup.

Further, data from trial 1245-0025 have been analysed, a cardiovascular outcome trial of empagliflozin compared to usual care on patients with T2DM with an increased cardiovascular risk.

In addition, data from trial 1218-0091 have been analysed, a double-blind, randomised, placebo-controlled trial in children and adolescents with T2DM. The trial included children and adolescents who had been diagnosed with T2DM and were treated with metformin and/or insulin or they were not tolerating metformin.

SIII.1 CLINICAL TRIAL 1218-0091

In trial 1218-0091, most patients took metformin (alone [51.0%] or in combination with insulin [40.1%]) as background antidiabetic treatment at baseline, with balanced distribution across treatment groups (CTR 1218-0091 [c38245139-01], Section 10.4.3).

53 patients received placebo and 52 patients empagliflozin. The total exposure amounted to 25.0 PY in the placebo group and 23.7 PY in the empagliflozin group. Both treatment groups comprised more female than male patients. With regard to ethnic origin, the largest proportion of patients in both treatment groups was White, followed by Black. An overview is given in the tables below.

SIII.Table 2 Duration of exposure (trial 1218-0091) - TS

	Placebo		All Empa[1]	
	Patients N (%)	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**
Cumulative exposure				
≥0 weeks	53 (100.0)	25.0	52 (100.0)	23.7
≥12 weeks	50 (94.3)	24.7	49 (94.2)	23.6
≥26 weeks	34 (64.2)	17.2	31 (59.6)	15.7

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: Jardiance EU-RMP v21.0 [s00017688-49], SIII.Table 2

SIII.Table 3 Age group and gender (trial 1218-0091) - TS

Gender/ Age group [years]	Placebo		All Empa[1]	
	Patients N	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
Male				
<65	19	9.3	19	9.0
Female				
<65	34	15.6	33	14.8

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: Jardiance EU-RMP v21.0 [s00017688-49], SIII.Table 3

SIII.Table 4 Ethnic origin (trial 1218-0091) - TS

Race	Placebo		All Empa[1]	
	Patients N	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
American Indian/Alaska Native	1	0.5	4	1.8
Asian	3	1.4	2	1.0
Black/African American	17	7.4	19	8.8
Native Hawaiian/Pacific Islander	1	0.5	0	0
White	29	14.6	23	10.2
Multiple	1	0.0	4	2.0

[1] All Empa contains empagliflozin 10 mg/25 mg of trial 1218-0091.

Data source: Jardiance EU-RMP v21.0 [s00017688-49], SIII.Table 4

SIII.2 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS (SAF-C4)

SAF-C4 comprised in total 1366 patients in the empa25mg+met arm; 1385 patients in the empa10mg+met arm; and 1034 patients in the placebo+met arm. The majority of patients were treated for ≥24 weeks, the percentages being comparable between the empa25+met and empa10+met arms and higher in the placebo-met arm. An overview is given in the table below.

SIII.Table 5 Duration of exposure (SAF-C4) - TS

	Empa25mg+met	Empa10mg+met	Placebo+met	All empa+met
	Number of patients, N (%)	**Number of patients, N (%)**	**Number of patients, N (%)**	**Number of patients, N (%)**
Cumulative exposure				
≥1 day	1366 (100.0)	1385 (100.0)	1034 (100.0)	2751 (100.0)
≥24 weeks	571 (41.8)	593 (42.8)	565 (54.6)	1164 (42.3)

Data source: data on file, R0690, Table 3.1.1

Both active treatment groups comprised fewer female than male patients; there was no notable difference between genders in the placebo+met arm. In all treatment groups, the largest proportion of patients was younger than 65 years. There were only 3 patients aged ≥85 years (1 patient in each treatment arm); these 3 patients were all male.

Exposure to trial medication was higher in the empagliflozin/metformin arms than the placebo+met arm for all race subgroups, due to the overall lower number of patients in the placebo+met arm. However, there was no notable difference between the empagliflozin/metformin arms. In all treatment groups, the majority of patients were White, followed by Asian and then Black patients.

Further details are given in the following tables.

SIII.Table 6 Age group and gender (SAF-C4) - TS

Gender/age group [years]	Empa25mg+met		Empa10mg+met		Placebo+met		All empa+met	
	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]
Male								
<65	579	224.0	582	227.1	413	169.4	1161	451.1
65–<75	147	54.0	142	52.0	89	34.9	289	106.0
75–<85	20	6.5	22	8.1	16	6.6	42	14.5
≥85	1	0.3	1	0.3	1	0.3	2	0.7
Female								
<65	485	185.6	491	190.0	418	168.0	976	375.6
65–<75	114	40.9	125	45.3	83	32.3	239	86.3
75–<85	20	6.7	22	7.4	14	5.4	42	14.1

Data source: data on file, R0690, Table 3.1.3

SIII.Table 7 Ethnic origin (SAF-C4) - TS

	Empa25mg+met		Empa10mg+met		Placebo+met		All empa+met	
	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]	Number of patients, N	Person-time [PY]
Race								
White	919	332.9	930	337.9	620	240.2	1849	670.8
Black/African American	61	22.4	65	21.6	43	14.8	126	43.9
Asian	363	154.5	360	159.8	348	153.1	723	314.4
Other	23	8.2	30	10.9	23	8.8	53	19.1

Data source: data on file, R0690; Table 3.1.4

SIII.3 CLINICAL TRIAL 1245-0025

Metformin subgroup of trial 1245-0025

In the metformin subgroup of this trial, 1734 patients received placebo, 1729 patients empagliflozin 10 mg, and 1730 patients empagliflozin 25 mg. The median exposure (including temporary off-treatment periods) in the placebo group was 2.60 years, 2.62 years in the empagliflozin 10 mg group, and 2.82 years in the empagliflozin 25 mg group. The empagliflozin groups comprised slightly higher proportions of patients with long exposure

times (i.e. ≥104 weeks and especially ≥156 weeks) than the placebo group. Consistent with these results, the total exposure amounted to 4369 years in the placebo group and about 4500 years in each of the empagliflozin groups. An overview is given in the table below.

SIII.Table 8 Exposure to randomised trial medication (metformin 1245-0025) - TS

	Empa 25 mg	Empa 10 mg	Placebo	All empa
Treated patients, N (%)	1730 (100.0)	1729 (100.0)	1734 (100.0)	3459 (100.0)
Exposure categories, N (%)				
≥12 weeks	1675 (96.8)	1668 (96.5)	1686 (97.2)	3343 (96.6)
≥26 weeks	1634 (94.5)	1640 (94.9)	1651 (95.2)	3274 (94.7)
≥52 weeks	1582 (91.4)	1571 (90.9)	1574 (90.8)	3153 (91.2)
≥78 weeks	1521 (87.9)	1508 (87.2)	1482 (85.5)	3029 (87.6)
≥104 weeks	1322 (76.4)	1310 (75.8)	1279 (73.8)	2632 (76.1)
≥156 weeks	762 (44.0)	746 (43.1)	702 (40.5)	1508 (43.6)
≥208 weeks	30 (1.7)	16 (0.9)	13 (0.7)	46 (1.3)
≥260 weeks	0	0	0	0
Exposure [years]				
Mean (SD)	2.61 (1.02)	2.58 (1.02)	2.52 (1.00)	2.60 (1.02)
Median	2.82	2.62	2.60	2.64
(Q10, Q90)[1]	(1.18, 3.70)	(1.06, 3.69)	(1.06, 3.68)	(1.15, 3.70)
Total exposure [years]	4518.7	4462.4	4369.3	8981.0

Exposure was calculated as date of last intake of trial medication minus date of first intake, plus 1 day. Interruptions of trial medication were ignored, i.e. considered as if patients had taken trial medication.

Q10 and Q90 represent the 10% and 90% quantiles.

Data source: SCS supplement [c08865050-01], Table 5.1

SIII.4 POOLED INDICATIONS

Adult and paediatric T2DM

The pooling SAF-C4+1245-0091 comprised 1087 patients receiving placebo and 2803 patients empagliflozin. The majority of patients were treated for ≥12 weeks. The total cumulative patient-time was higher in the empagliflozin treatment group than for placebo. An overview of cumulative exposure is given in SIII.Table 9.

The active treatment groups comprised fewer female than male patients. The largest proportion of patients was younger than 65 years in both the male and female groups with a comparable distribution across age categories within the respective male and female groups. Further details are given in SIII.Table 10.

With regard to ethnic origin, the largest proportion of patients in either treatment group was White, followed by Asian. A tabular overview is given in SIII.Table 11.

SIII.Table 9 Duration of exposure (SAF-C4+1218-0091) - TS

	Placebo		Empa 10mg		Empa 25mg		All empa	
	Patients N (%)	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**	**Patients N (%)**	**Person-time [PY]**
Cumulative exposure								
≥0 weeks	1087 (100.0)	637.7	1385 (100.0)	737.1	1366 (100.0)	717.2	2803 (100.0)	1478.1
≥12 weeks	1032 (94.9)	632.0	1322 (95.5)	730.4	1298 (95.0)	710.1	2669 (95.2)	1464.1
≥26 weeks	298 (27.4)	309.9	265 (19.1)	303.2	260 (19.0)	294.2	556 (19.8)	613.2
≥52 weeks	204 (18.8)	252.3	208 (15.0)	263.3	202 (14.8)	252.1	410 (14.6)	515.4
≥78 weeks	64 (5.9)	96.4	78 (5.6)	117.8	70 (5.1)	105.3	148 (5.3)	223.1

All Empa contains Empa 10mg, Empa 25mg as well as Empa10/Empa25mg of trial 1218-0091.

Data source: data on file, Synjardy-rmp-exposure-outputs-r2272, Table 1.1.1

SIII.Table 10 Age group and gender (SAF-C4+1218-0091) - TS

	Placebo		Empa 10mg		Empa 25mg		All empa	
Gender/age group [years]	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
Male								
<65	432	255.7	582	314.7	579	292.2	1180	615.9
65–<75	89	50.8	142	72.9	147	82.4	289	155.3
75–<85	16	7.6	22	10.6	20	9.0	42	19.6
≥85	1	0.3	1	0.3	1	1.5	2	1.8
Female								
<65	452	257.8	491	265.7	485	263.4	1009	543.9
65–<75	83	55.3	125	61.4	114	58.9	239	120.3
75–<85	14	10.2	22	11.5	20	9.8	42	21.3

All Empa contains Empa 10mg, Empa 25mg as well as Empa10/Empa25mg of trial 1218-0091.

Data source: data on file, Synjardy-rmp-exposure-outputs-r2272, Table 1.1.8

SIII.Table 11 Ethnic origin (SAF-C4+1218-0091) - TS

	Placebo		Empa 10mg		Empa 25mg		All empa	
Race	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**	**Patients N**	**Person-time [PY]**
American Indian/Alaska Native	19	9.8	28	11.3	20	8.6	52	21.7
Asian	351	174.8	360	185.9	363	174.2	725	361.0
Black/African American	60	32.8	65	32.3	61	34.0	145	75.0
Native Hawaiian/ Pacific Islander	6	3.9	2	0.9	3	0.8	5	1.8
White	649	415.8	930	506.7	919	499.6	1872	1016.5
Multiple	1	0.0	0	0.0	0	0.0	4	2.0

All Empa contains Empa 10mg, Empa 25mg as well as Empa10/Empa25mg of trial 1218-0091.

Data source: data on file, Synjardy-rmp-exposure-outputs-r2272, Table 1.1.11

SIII.5 REFERENCES

SIII.5.1 Published references

Not applicable.

SIII.5.2 Unpublished references

c08865050-01 Summary of Clinical Safety – Supplement. 21 Jan 2016

c38245139-01 A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus (DINAMO™, main trial). 1218-0091. 10 Nov 2022

s00017688-49 Risk Management Plan for Jardiance, version 21.0. 22 Nov 2022

ABBREVIATIONS

CTR	Clinical Trial Report
DINAMO	Study acronym; DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents
Empa	Empagliflozin
EMPA-REG OUTCOME	Study acronym; EMPAgliflozin Removal of Excess of Glucose OUTCOME trial
EU	European Union
Met	Metformin
PY	Patient-years
RMP	Risk Management Plan
SAF	Safety analysis set
SCS	Summary of clinical safety
SD	Standard deviation
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TS	Treated set

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Synjardy 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

Synjardy 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

Synjardy 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

Synjardy 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

SVIII.Table 1 Summary of safety concerns

Important identified risks	Lactic acidosis[1]
Important potential risks	None
Missing information	None

[1] Safety concern derived from the mono compound metformin.

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

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- Lactic acidosis

Other forms of routine pharmacovigilance activities for:
None.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing and planned additional pharmacovigilance activities.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Synjardy 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 SYNJARDY (EMPAGLIFLOZIN+METFORMIN)

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

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

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

I. THE MEDICINE AND WHAT IT IS USED FOR

Synjardy is authorised in adults and children aged 10 years and above for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains empagliflozin and metformin as the active substances and it is given by oral administration.

Further information about the evaluation of Synjardy's benefits can be found in Synjardy'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

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

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

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

Together, these measures constitute routine risk minimisation measures.

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

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

II.A List of important risks and missing information

Important risks of Synjardy 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 Synjardy. 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[1]
Important potential risks	None
Missing information	None

[1] Safety concern derived from the mono compound metformin.

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 Synjardy.

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

There are no studies required for Synjardy.

ABBREVIATIONS

EMA	European Medicine Agency
EPAR	European Public Assessment Report

PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus

PART VII APPENDICES

PART VII TABLE OF CONTENTS

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Appendix - Table of Contents

Questionnaire: Lactat acidosis- Synjardi-Questionnaire - V 10.0

Questionnaire questions (Q:)

Context in LSMV = Questionnaire

Question ID	Questionnaire Name	Question
Q:LAS01	Lactic Acidosis Event Form (Synjardy)	Risk factors [Yes ; No; If yes, if possible please provide time/date in relation to lactic acidosis event; Amount] - Any history of alcohol use - Any exposure to contrast media in the last - Any Infection/Sepsis - Any Renal disease: Acute or Chronic [If stage of chronic renal disease known please specify] - Dehydration [Severity] - Diarrhoea [Severity] - Vomiting [Severity]
Q:LAS02	Lactic Acidosis Event Form (Synjardy)	Cardiac Risk factors [Yes ; No; If yes, if possible please provide time/date in relation to lactic acidosis event; Amount] - Acute heart failure - Acute myocardial infarction - Other conditions causing hypoxia
Q:LAS03	Lactic Acidosis Event Form (Synjardy)	Metformin information [Daily dose of Metformin, value/unit; Last dose of Metformin, value/unit; date/time]
Q:LAS04	Lactic Acidosis Event Form (Synjardy)	Other Concomitant Medication Name [Start date; Stop date (if medication not ongoing at the time of event); Comment (if applicable)]

Questionnaire: Lactat acidosis- Synjardi-Questionnaire - V 10.0

Q:LAS05	Lactic Acidosis Event Form (Synjardy)	Lab Parameter [Date; Value/Unit; Reference Range] - Renal function (before lactic acidosis): eGFR,S.creatinine - Renal function (during lactic acidosis): eGFR,S.creatinine - Lactate level - Blood pH (arterial or venous) - β-hydroxybutyrate (blood) - Ketone (urine) - Anion Gap - Metformin plasma level - Metformin concentration in erythrocytes - Other:
Q:LAS06	Lactic Acidosis Event Form (Synjardy)	Please specify any of the above information used to confirm the diagnosis of lactic acidosis.
Q:LAS07	Lactic Acidosis Event Form (Synjardy)	Treatment for the event [Yes; No; Comment (if applicable)] - Fluid replacement - Sodium bicarbonate - Hemodialysis - Other therapies:

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

There are no proposed additional risk minimisation activities for Synjardy.