Summary of the risk management plan for Jardiance (empagliflozin)

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

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

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

I. The medicine and what it is used for

Jardiance is authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains empagliflozin as the active substance and it is given by oral administration.

Further information about the evaluation of Jardiance’s benefits can be found in Jardiance’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 Jardiance, together with measures to minimise such risks and the proposed studies for learning more about Jardiance'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 Jardiance is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Jardiance 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 Jardiance. 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	Complicated urinary tract infection
	Genital infection
	Diabetic ketoacidosis with atypical presentation
Important potential risks	Urinary tract carcinogenicity
	Liver injury
	Bone fracture
	Amputation risk
	Pancreatitis
Missing information	Pregnancy/breast-feeding

II.B Summary of important risks

Important identified risks

Complicated urinary tract infection	
Evidence for linking the risk to the medicine	An increased urinary glucose excretion may predispose to UTIs in general, which may ascend to infect the kidney and be complicated with urosepsis. This effect may be counterbalanced with the increased urinary flow due to the osmotic diuresis. In randomised, placebo-controlled, clinical trials, the incidence of overall complicated UTI, serious UTI, and pyelonephritis was low and similar between empagliflozin and placebo. More patients treated with empagliflozin discontinued due to UTI; and more events assessed as related to treatment were reported in patients treated with empagliflozin. More patients treated with empagliflozin experienced urosepsis than in the placebo group; however, the number of patients was low. Overall, clinical trial data on urosepsis and post-marketing experience suggest that treatment with empagliflozin may increase the risk of pyelonephritis and urosepsis. Further evaluation in ongoing clinical trials and a dedicated non-interventional PASS (1245.96) is ongoing.
Risk factors and risk groups	The clinical trial data of empagliflozin are in agreement with the known risk factors for UTI: • Female gender • Sexually active females tend to have more UTIs than women who are not sexually active • Females who use diaphragms for birth control may be at higher risk, as may women who use spermicidal agents • After menopause, UTIs may become more common because the lack of oestrogen causes changes in the urinary tract that make it more vulnerable to infection • Kidney stones may be associated with an increased risk of complicated UTIs • Prostatic enlargement may be associated with urinary retention in the bladder may increase the risk of UTI • Diabetes and other diseases that impair the immune system may increase the risk of UTIs

	• Instrumentation with a catheter to urinate may increase the risk of UTIs • Asymptomatic bacteriuria In clinical trials with empagliflozin, the frequency of patients with UTI was higher in all treatment groups in female patients, in patients with renal impairment, in patients aged >75 years, and in patients with a history of UTI. UTIs are a common comorbidity in patients with diabetes. Observational studies of patients with diabetes and infection suggest that they seem to be more likely to progress to bloodstream infections and sepsis than patients with infection but no diabetes. The IR of various UTIs in T2DM patients in Europe and North America between 1990 and 2011 were comprised between 46.9 and 101 per 1000 PY. The IR of pyelonephritis in T2DM was measured between 3 and 4.9 per 1000 PY.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.96 See Section II.C of this summary for an overview of the post-authorisation development plan.
Genital infection	
Evidence for linking the risk to the medicine	An increased urinary glucose excretion may predispose to genital infection. This effect may be counterbalanced with an increased urinary flow due to osmotic diuresis. In randomised, placebo-controlled, clinical trials the incidence of genital infections was comparable between empagliflozin and placebo groups; more patients treated with empagliflozin discontinued due to genital infection; and more events assessed as related to the treatment were reported in patients treated with empagliflozin. Genital infection is considered a class-effect for all SGLT-2 inhibitors. Further characterisation of the risk will be provided from the ongoing PASS (1245.96).
Risk factors and risk groups	The clinical trial data of empagliflozin are in agreement with the known risk factors for genital infection:

	• Female gender • Sexually active females tend to have more genital infections than women who are not sexually active • Females who use diaphragms for birth control may be at higher risk, as may women who use spermicidal agents • After menopause, genital infections may become more common because the lack of oestrogen causes changes in the genital that make it more vulnerable to infection • Diabetes and other diseases that impair the immune system may increase the risk of genital infection In clinical trial with empagliflozin the frequency of patients with genital infection was higher in female patients and in patients with a history of genital infection. Information on incidence estimates for genital infections in patients with T2DM is very limited and is not available for most countries other than UK and US, although they seem to be rather common. No data was found in genital infection in T1DM specifically. Available data in T2DM suggests incidence of male genital infections between 8 and 13 per 1000 PY, and female genital infections – between 2 and 21 per 1000 PY, with reasons for this discrepancy yet to be clarified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.96 See Section II.C of this summary for an overview of the post-authorisation development plan.

Diabetic ketoacidosis with atypical presentation

Evidence for linking the risk to the medicine	Clinical trial data of empagliflozin did not show an increased risk of DKA. Pre-clinical and clinical data show that treatment with empagliflozin increased blood ketone levels. During post-marketing, cases of DKA were reported. Epidemiological data show that the risk of DKA is higher in patients treated with SGLT-2 inhibitors. Further characterisation of the risk will be provided from the ongoing PASSs (1245.96 and

	1245.146). DKA with atypical presentation is considered a class-effect of all SGLT-2 inhibitors. In situations with predisposing factors, temporary treatment interruption of empagliflozin may be required. DKA can be severe and even fatal.
Risk factors and risk groups	Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. T1DM patients, T2DM patients with low C-peptide or LADA or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT-2 inhibitors should be used with caution in these patients. DKA occurs mainly in patients with T1DM but patients with T2DM are also susceptible, especially under stressful conditions such as trauma, surgery, infections, or problems related to insulin therapy. The incidence of DKA episodes varies highly according to age groups and race: from 1.4 to 14.3 per 1000 PY in Caucasian patients with DM, to 22.7 per 1000 PY in African-Americans. DKA is a common complication among adult patients with T1DM; however, specific population-based estimates on the incidence and prevalence of DKA in T1DM have rarely been reported. One identified study conducted in the US and Canada found that the IR of DKA in T1DM ranged from zero per 1000 PY to 31 per 1000 PY, depending on study group and time period.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.96, PASS 1245.146 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks

Urinary tract carcinogenicity	
Evidence for linking the risk to the medicine	The potential risk of renal cancer is based on toxicology findings and bladder cancer due to observations from other SGLT-2 inhibitors: 1. Dapagliflozin data showed an imbalance for human bladder (and previously also breast cancer) as presented at US FDA Advisory Committee and also in the EPAR on dapagliflozin (EMA homepage). 2. Carcinogenicity studies with empagliflozin showed occurrence of renal malignancy in male CD-1 mice, not in female mice. The CD-1 mouse strain is characterised by increased background of renal malignancy. The empagliflozin-related renal tumours occurred only in male mice given 1000 mg/kg/day, which resulted in systemic exposure approximately 30-fold higher than exposure associated with the 25 mg/day dose in humans. Carcinogenicity studies in rat did not reveal renal malignancy. Empagliflozin is not genotoxic. Research into the mode of action for the male mouse renal tumours revealed them to be secondary to several sources of chronic and persistent tubular degeneration. These sources include a natural predisposition of the aged male mouse to renal pathology, exacerbation of background renal tubular dilatation and cystic hyperplasia induced by chronic osmotic diuresis, metabolic stress due to a predominantly oxidative metabolism, production of a cytotoxic metabolite predominant in the male mouse, and consequent exhaustion of tubular epithelial oxidative detoxication. Reparative tubular epithelial cell proliferation is observed in male mice, but not female mice indicating the specificity of the sequence of events for the male CD-1 mouse. Ultimately over the course of 2 years of treatment, these key events lead to a constitutive focal proliferative phenotype and a low incidence of renal tumours appearing late in life. Based on this research, the weight of evidence on genotoxicity, gender and mouse strain specificity, and the dose response and temporal relationships of chronic sustained non-neoplastic degenerative/regenerative tubular changes with renal neoplasms, the renal

	tumours observed in mice are considered irrelevant for humans. The safety margin relative to the 25 mg/day dose of empagliflozin further mitigates uncertainties regarding the human relevance of the single-gender liability observed in the mouse. Aside from the expected pharmacology of SGLT-2 inhibition in clinical trials with empagliflozin, there is no evidence of safety risks for drug-related renal injury (biomarkers of glomerular or tubular damage, permanent or progressive reduction in renal function) or renal cancers. Malignancy is a serious condition which may have serious complications (including due to the required treatment), and decrease the quality of life. Further characterisation of the risk will be provided from the ongoing PASS (1245.97).
Risk factors and risk groups	Risk factors for bladder cancer are smoking, exposure to aromatic amines or aniline dyes, history of radiation treatment of the pelvis, chemotherapy with cyclophosphamide, and long-term indwelling urinary catheterisation. Risk factors for renal cancer are smoking, obesity, hypertension, exposure to substances such as asbestos, cadmium, benzene, and genetic hereditary diseases such as von Hippel-Lindau disease, Birt-Hogg-Dube syndrome.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.97 See Section II.C of this summary for an overview of the post-authorisation development plan.
Liver injury	
Evidence for linking the risk to the medicine	In clinical trials, more patients treated with empagliflozin than with placebo were reported with ALT and/or AST elevations of >5x ULN. However, the overall occurrence of liver injuries in patients treated with empagliflozin was not increased. DILI is considered an important medical condition which leads to treatment discontinuation of empagliflozin and may require hospitalisation and dedicated treatment. Further characterisation of the risk will be provided from the

	ongoing PASS (1245.96).
Risk factors and risk groups	Risk groups include patients on hepatotoxic drugs (such as non-steroidal anti-inflammatories, carbamazepine, isoniazid, statins), with chronic liver disease (such as fatty liver disease and viral hepatitis infections), and with diabetes.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.4 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.96 See Section II.C of this summary for an overview of the post-authorisation development plan.
Bone fracture	
Evidence for linking the risk to the medicine	Bone fracture is defined as an important identified risk for another SGLT-2 inhibitor. Bone fractures might lead to incapacity and/or reduce quality of life.
Risk factors and risk groups	Risk groups include patients with advanced age, post-menopausal women, and smokers. The most important risk factors include low BMD, long term glucocorticoid therapy, cigarette smoking, excess alcohol intake, high levels of bone turnover markers, and parental history of hip fracture.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None
Amputation risk	
Evidence for linking the risk to the medicine	An increase in cases of LLA (primarily of the toe) has been observed in long-term clinical trials with another SGLT-2 inhibitor. This has not been observed in empagliflozin clinical trials but is unknown whether this constitutes a class effect. Further characterisation of the risk will be provided from the planned PASS (1245.171).
Risk factors and risk groups	The risk of amputations is increased in people with diabetes who have the following risk factors: cigarette smoking, history of foot ulcer or previous amputation, foot deformities including pre-ulcerative callus or corn, Charcot foot, peripheral neuropathy with loss of

	protective sensation, peripheral artery disease, poor glycaemic control, visual impairment due to diabetic retinopathy and diabetic nephropathy (especially patients on dialysis)
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1245.171 See Section II.C of this summary for an overview of the post-authorisation development plan.
Pancreatitis	
Evidence for linking the risk to the medicine	In clinical trials, there was no increase in the frequency of pancreatitis AEs with empagliflozin treatment compared to placebo. However, these results have limitations due to the relatively small sample size to for capturing rare events. Within post-authorisation experience, the information received does not provide strong evidence for a causal association between empagliflozin treatment and pancreatitis. Most of the case reports contain very limited information to allow for a causality assessment. In most of the remaining cases, concomitant conditions or drugs, or medical history provide an alternative aetiology of the event. In few cases, no alternative cause was reported among the concomitant or past diseases or drugs; in none of these cases rechallenge was performed. Considering that post-marketing cases were received in which the causal association with pancreatitis cannot be completely excluded, 'pancreatitis' is proposed to be included as an important potential risk. A PASS is planned to be conducted to further investigate this potential risk.
Risk factors and risk groups	Patients with T2DM have an increased risk for pancreatitis. Further, obesity, history of alcohol use, history of smoking, higher comorbidity index, hypertriglyceridemia, and any history of gallbladder disease are important risk factors of acute pancreatitis. Results of a retrospective cohort study using data from 2007 to 2009 of a large US medical and pharmacy

	claims database also show a higher percentage of biliary stone disease and hypertriglyceridemia among patients with diabetes compared to patients without diabetes. Biliary stone disease was diagnosed in 0.84% of the diabetics compared to 0.60% in the non-diabetics (p<0.0001). The respective numbers for hypertriglyceridemia were 1.71% vs. 0.95% (p<0.0001).
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None

Missing information

Pregnancy/breast-feeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Prescription only medicine Additional risk minimisation measures: None

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 Jardiance.

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

PASS 1245.96
Purpose of the study: To evaluate the risk of urinary tract and genital infection, acute renal and hepatic injury, and diabetic ketoacidosis resulting in hospitalisations, in empagliflozin-treated patients, compared to users of other antidiabetic treatment

PASS 1245.97
Purpose of the study: To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment

PASS 1245.146
Purpose of the study: To evaluate the risk of diabetic ketoacidosis in patients treated with empagliflozin

PASS 1245.171
Purpose of the study: Meta-analysis to evaluate amputation risk in trials 1245.25, 1245.110, 1245.121

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMD	Bone mineral density
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
IR	Incidence rate
LLA	Lower limb amputation
PASS	Post-authorisation safety study
PSUR	Periodic Safety Update Report
PY	Patient-year
RMP	Risk Management Plan
SGLT-2	Sodium-dependent glucose co-transporter 2
SmPC	Summary of Product Characteristics
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
vs.	Versus