PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR QTERN (SAXAGLIPTIN/DAPAGLIFLOZIN FDC)

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

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

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

THE MEDICINE AND WHAT IT IS USED FOR

QTERN is authorised in adults aged 18 years and older with type 2 diabetes mellitus (see SmPC for the full indication). It contains saxagliptin and dapagliflozin as the active substances and it is given by oral route of administration.

Further information about the evaluation of QTERN's benefits can be found in QTERN's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/qtern.

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

Important risks of QTERN, together with measures to minimise such risks and the proposed studies for learning more about QTERN'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 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 QTERN is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of QTERN 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 QTERN. 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).

Table 1 List of important risks and missing information

Important identified risks	Diabetic ketoacidosis including events with atypical presentation (dapagliflozin component)
Important potential risks	Severe cutaneous adverse reactions (saxagliptin component) Pancreatic cancer (saxagliptin component) Bladder cancer (dapagliflozin component) Breast cancer (dapagliflozin component) Prostate cancer (dapagliflozin component) Lower limb amputation (dapagliflozin component)
Missing information	None

Summary of important risks

Table 2 Important identified risk – diabetic ketoacidosis including events with atypical presentation

Evidence for linking the risk to the medicine	Post-marketing experience with use of SGLT2 inhibitors, including dapagliflozin. DKA including events with atypical presentation is an important identified risk for dapagliflozin.

Table 2 Important identified risk – diabetic ketoacidosis including events with atypical presentation

Risk factors and risk groups	Risk factors such as post-operative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet), loss of appetite due to e.g., gastrointestinal infection, depression or malaise; severe infections or other severe medical conditions such as myocardial infarction and stroke; and pancreatic insufficiencies due pancreatitis, cancer or alcohol abuse.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. SmPC section 4.4 where it is stated that QTERN should be discontinued if DKA is suspected or diagnosed. PL sections 2 and 4.
Additional pharmacovigilance activities	Externally sponsored independent investigator initiated nonclinical mechanistic model studies (postdoc project) [dapagliflozin component]

Table 3 Important potential risk – severe cutaneous adverse reactions

Evidence for linking the risk to the medicine	Post-marketing experience from DPP-4 inhibitors, including saxagliptin. Severe cutaneous adverse reactions is an important potential risk for saxagliptin.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: Monitoring for skin disorders, such as blistering, ulceration or rash, is recommended (SmPC section 4.4). Recommendation to follow instructions from HCP regarding skin care (PL section 2).

Table 4 Important potential risk – pancreatic cancer

Evidence for linking the risk to the medicine	The potential risk of pancreatic cancer has been discussed in published literature and evaluated by health authorities for the class as well as for other incretin-based antidiabetics (GLP- 1 analogues). Pancreatic cancer is an important potential risk for saxagliptin.
Risk factors and risk groups	There is an increase in risk of pancreatic cancer among patients with T2DM. Age, gender, race, cigarette smoking, obesity, diabetes, chronic pancreatitis, cirrhosis of the liver, occupational exposure, family history, and infections of the stomach with the ulcer causing bacteria *Helicobacter pylori* are other known risk factors.
Risk minimisation measures	No risk minimisation measures

Table 5 Important potential risk – bladder cancer

Evidence for linking the risk to the medicine	Clinical trial data with dapagliflozin. Bladder cancer is an important potential risk for dapagliflozin.
Risk factors and risk groups	Age, gender (male), smoking (now or ever), chemical exposure to know carcinogens (cyclophosphamide and aniline dyes etc), and haematuria
Risk minimisation measures	None
Additional pharmacovigilance activities	MB102118 (dapagliflozin) – Comparison of the risk of cancer between patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies.

Table 6 Important potential risk – breast cancer

Evidence for linking the risk to the medicine	Clinical trial data with dapagliflozin. Breast cancer is an important potential risk for dapagliflozin.
Risk factors and risk groups	Age, gender (female), smoking (now or ever), parity, use of exogenous estrogen (i.e., hormone replacement therapy), BRCA1 or BRCA2 mutations, family history of breast cancer, breast tissue density, overweight/obesity.
Risk minimisation measures	None
Additional pharmacovigilance activities	MB102118 (dapagliflozin) – Comparison of the risk of cancer between patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies.

Table 7 Important potential risk – prostate cancer

Evidence for linking the risk to the medicine	Clinical trial data with dapagliflozin. Prostate cancer is an important potential risk for dapagliflozin.
Risk factors and risk groups	Age, smoking.
Risk minimisation measures	None
Additional pharmacovigilance activities	MB102118 (dapagliflozin) – Comparison of the risk of cancer between patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies.

Table 8 Important potential risk – lower limb amputation

Evidence for linking the risk to the medicine	Clinical trial data with another SGLT2 inhibitors. Lower limb amputations is an important potential risk for dapagliflozin.
Risk factors and risk groups	Amputation is a treatment that is preceded by multiple diseases. Subjects with diabetes are at high risk for amputation due to a high prevalence of cardiovascular disease, including peripheral arterial disease, dyslipidaemia, peripheral neuropathy, and chronic kidney disease. Minor trauma can be an increased risk due to existing neuropathy and may led to ulcers that get infected and do not heal. The non-healing, infected ulcers may lead to gangrene and amputation.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and PL section 2.
Additional pharmacovigilance activities	Dedicated eCRF for Lower Limb Amputation will be evaluated in studies D169AC00001, D169CC00001, D169EC00001, D169EC00002.

Post-authorisation development plan

There are no ongoing or planned additional pharmacovigilance studies or activities for QTERN.

Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligations of QTERN.

Other studies in post-authorisation development plan

There are no studies required for QTERN. The pharmacovigilance activities listed below are planned or ongoing for the mono-component products, saxagliptin and dapagliflozin, and are included in this RMP as the results will potentially provide information relevant to the safety profile of QTERN. The information below is provided for information purpose only and these studies will be maintained through the respective mono-component RMPs.

Saxagliptin

None

Dapagliflozin

Study short name: MB102118 (D1690R00007) – Cancer in Patients on Dapagliflozin [Observational study].

Purpose of the study: (1) To compare the incidence of breast cancer, by insulin use at cohort entry, among females with T2DM who are new initiators of dapagliflozin and females who are new initiators of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or SU monotherapy and (2) To compare the incidence of bladder cancer, by insulin use and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin and those who are new initiators of antidiabetic drugs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or SU monotherapy.

Study short name: D169CC00001 Deliver

Purpose of the study: Evaluate the effect of dapagliflozin on reducing cardiovascular death or worsening heart failure in patients with HFpEF. Study includes additional eCRF related to risk of lower limb amputation.

Externally sponsored independent investigator initiated nonclinical mechanistic model study (postdoc project)

Purpose of the study: Study aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.