Forxiga®

5 mg and 10 mg film-coated tablets

Summary of the Risk Management Plan (RMP) for Forxiga® (dapagliflozin)

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Forxiga® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Forxiga® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Forxiga®.

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

FORXIGA'S Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FORXIGA should be used.

This summary of the RMP for FORXIGA 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 FORXIGA'S RMP.

I.1 THE MEDICINE AND WHAT IT IS USED FOR

FORXIGA is authorised in adult patients for treatment of type 2 diabetes mellitus as an adjunct to diet and exercise, for treatment of symptomatic chronic heart failure with reduced ejection fraction and patients with chronic kidney disease. It contains dapagliflozin as the active substance and it is given orally.

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

FORXIGA
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga

I.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FORXIGA, together with measures to minimise such risks and the proposed studies for learning more about FORXIGA'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 as 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 the routine risk minimisation measures.

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

I.2.1 List of important risks and missing information

Important risks of FORXIGA 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 FORXIGA. 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
Important potential risks	Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV

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

Evidence for linking the risk to the medicine	Postmarketing experience with use of SGLT2 inhibitors, including dapagliflozin. In clinical studies with T1DM, there was a higher number of diabetic ketoacidosis (DKA) in the dapagliflozin-treated patients compared to placebo. DKA was also reported in the T2DM DECLARE study with rare frequency.
Risk factors and risk groups	Postoperative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet); loss of appetite due to, eg, 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 minimisations measures: SmPC sections “Warnings and precautions”, “Undesirable effects” PL sections 2, 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section “Warnings and precautions”, PL section “When is caution required when taking Forxiga?”).

	Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section "Warnings and precautions").
Additional pharmacovigilance activities	Nonclinical mechanistic model studies (postdoc project). (dapagliflozin). See section I.2.2 of this summary for an overview of the post-authorisation development plan.

Table -3 Important potential risk – Bladder cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, sex (male), smoking (now or ever), chemical exposure to known carcinogens (cyclophosphamide and aniline dyes, etc), and haematuria.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section I.2.2 of this summary for an overview of the post-authorisation development plan.

Table -4 Important potential risk – Breast cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, sex (female), smoking (now or ever), parity, use of exogenous oestrogen (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: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section I.2.2 of this summary for an overview of the post-authorisation development plan.

Table -5 Important potential risk – Prostate cancer

Evidence for linking the risk to the medicine	Clinical trial data with use of dapagliflozin.
Risk factors and risk groups	Age, smoking.
Risk minimisation measures	None.
Additional pharmacovigilance activities	MB102118: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment See section I.2.2of this summary for an overview of the post-authorisation development plan.

Table -6 Important potential risk – Lower limb amputation

Evidence for linking the risk to the medicine	Clinical trial data for another SGLT2 inhibitor.
Risk factors and risk groups	Subjects with diabetes are at high risk for amputation due to a high prevalence of CV disease, including PAD, 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 activities: SmPC section "Warnings and precautions": Guidance provided on potential class effect PL section "When is caution required when taking Forxiga?": Counsel on routine preventative foot care.
Additional pharmacovigilance activities	Dedicated eCRF for Lower Limb Amputation is evaluated in studies D169AC00001, D169CC00001, D169EC00001, D169EC00002. See section I.2.2 of this summary for an overview of the post-authorisation development plan.

Table -7 Missing information – Use in patients with NYHA class IV

Risk minimisation measures	Routine risk minimisation measures: SmPC Section: "Warnings and precautions"

I.2.2 Post-authorisation development plan

Studies which are conditions of the marketing authorisation

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

I.2.2.1 Other studies in post-authorisation development plan

Study short name: Nonclinical mechanistic model studies [Postdoc project].

Purpose of the study: Studies 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.

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 heart failure with preserved ejection fraction (HFpEF).