SUMMARY OF THE RISK MANAGEMENT PLAN

I: SUMMARY OF THE RISK MANAGEMENT PLAN FOR ONGLYZA™ (SAXAGLIPTIN) AND KOMBOGLYZE™ (SAXAGLIPTIN+METFORMIN FDC)

This is a summary of the risk management plan (RMP) for ONGLYZA (saxagliptin) and KOMBOGLYZE (saxagliptin+metformin FDC). The RMP details important risks of ONGLYZA and KOMBOGLYZE, how these risks can be minimized, and how more information will be obtained about ONGLYZA's and KOMBOGLYZE's risks and uncertainties (missing information).

ONGLYZA's and KOMBOGLYZE's Summary of product characteristics (SmPC) and its Package leaflet give essential information to healthcare professionals and patients on how ONGLYZA and KOMBOGLYZE should be used.

This summary of the RMP for ONGLYZA and KOMBOGLYZE 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 ONGLYZA's and KOMBOGLYZE 's combined RMP.

I: 1 THE MEDICINE AND WHAT IT IS USED FOR

ONGLYZA is authorised for type 2 diabetes mellitus (see SmPC for the full indication). It contains saxagliptin as the active substance and it is given orally.

Further information about the evaluation of ONGLYZA’s benefits can be found in ONGLYZA’s European public assessment report (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/onglyza

KOMBOGLYZE:

KOMBOGLYZE is authorised for type 2 diabetes mellitus (see SmPC for the full indication). It contains saxagliptin and metformin as the active substances and it is given orally.

Further information about the evaluation of KOMBOGLYZE’s benefits can be found in KOMBOGLYZE’s European public assessment report (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/komboglyze

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

Important risks of ONGLYZA and KOMBOGLYZE together with measures to minimise such risks and the proposed studies for learning more about ONGLYZA's and KOMBOGLYZE'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.

I: 2.1 List of important risks and missing information

Important risks of ONGLYZA and KOMBOGLYZE are risks that need special risk management activities to further investigate or minimize 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 ONGLYZA and KOMBOGLYZE. 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 I-1 List of important risks and missing information

Type of safety concern	Safety concern
Important identified risks	Lactic acidosis (metformin component, saxagliptin + metformin FDC only)
Important potential risks	Severe cutaneous adverse reactions (saxagliptin component) Pancreatic cancer (saxagliptin component)
Missing information	Use in pregnancy and breastfeeding (saxagliptin component)

I: 2.2 Summary of important risks

Table I-2 Important identified risk: Lactic acidosis (metformin component, saxagliptin+metformin FDC only)

Evidence for linking the risk to the medicine	Post-marketing experience with use of metformin, as well as literature data.
Risk factors and risk groups	Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. Risk factors include poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function. High overdose of metformin or concomitant risks may lead to lactic acidosis. Elderly patients may be at high risk as this population is likely to have decreased renal function.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9. PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.2, 4.3,4.4, 4.5, 4.9 and PL section 2 and 4). Additional risk minimisation measures: None

Table I-3 Important potential risk: Severe cutaneous adverse reactions (saxagliptin component)

Evidence for linking the risk to the medicine	Post-marketing experience from DPP-4 inhibitors. The incidence of severe cutaneous adverse reactions (SCAR) was low and infrequent across the clinical programme and was generally similar between placebo and comparator. Isolated spontaneous reports of SCAR have been received from postmarketing use.
Risk factors and risk groups	Not known
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, PL section 2. Additional risk minimization measures: None

Table I-4 Important potential risk: Pancreatic cancer (saxagliptin component)

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).
Risk factors and risk groups	There is an increase in risk of pancreatic cancer among patients with T2DM. Age, gender, race, cigarette smoking, obesity, chronic pancreatitis, cirrhosis of the liver, occupational exposure, family history, and infection of the stomach with the ulcer causing bacteria Helicobacter pylori are other known risk factors.
Risk minimisation measures	No risk minimisation measures.

Table I-5 Missing information: Use in Pregnancy and Breastfeeding (saxagliptin component)

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6, PL Section 2. **Saxagliptin+metformin:** Routine risk minimisation measures: SmPC section 4.3 and 4.6, PL Section 2. Additional risk minimisation measures: None.

I: 2.3 Post-authorization development plan

I: 2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of ONGLYZA and KOMBOGLYZE.

I: 2.3.2 Other studies in post-authorisation development plan

There are no studies required for ONGLYZA and KOMBOGLYZE.