PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

I. Summary of Risk Management Plan For Ristfor

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

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

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

I.A The Medicine and What It Is Used For

Ristfor is authorised for treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Ristfor is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Ristfor is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Ristfor is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Refer to SmPC for the full indication.

It contains sitagliptin phosphate and metformin hydrochloride as the active substances and it is given by oral route of administration.

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001235/human_med_001330.jsp&mid=WC0b01ac058001d124

I.B Risks Associated with The Medicine and Activities to Minimise or Further Characterise The Risks

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

I.B.1 List of Important Risks and Missing Information

Important risks of Ristfor 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 Ristfor. 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.B.1.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

Ristfor has been marketed for 11 years since 2007 with over 25 million patient-years of treatment. The safety profile has been well-characterised during that time and adverse reactions that have been reported from clinical trials, non-interventional studies and post-approval safety surveillance analysis are included in the SmPC. There are no studies planned or warranted to further characterise any identified or potential risk that would alter the established risk-benefit profile for Ristfor. There are no additional important safety concerns for which prospective additional risk management is to be planned.

In conclusion, continued spontaneous safety surveillance and use of a lactic acidosis questionnaire as part of the routine pharmacovigilance activities will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimisation.

I.B.2 Summary of Important Risks

Table I.B.2.1: Important Identified Risk: Lactic Acidosis

Evidence for linking the risk to the medicine	Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin FDC; when it occurs, it is fatal in approximately 50% of cases. 2011 Sitagliptin in Combination with Metformin Pooled Safety Population
Risk factors and risk groups	The most common risk factor is renal insufficiency. Lactic acidosis may occur in association with other risk factors including poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Risk minimisation measures	Routine pharmacovigilance with use of a targeted questionnaire SmPC: Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects

Table I.B.2.2: Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	In clinical studies (2011 Sitagliptin in Combination with Metformin Pooled Safety Population; P082) there was no significant difference between treatment groups in the incidence of pancreatic malignancies, however, the clinical trials were not specifically designed to fully investigate pancreatic cancer as a safety concern.
Risk factors and risk groups	The risk of pancreatic cancer was significant for type 2 diabetes patients (adjusted HR 1.80 (95% Cl: 1.52, 2.14)), thus 80% increase in the risk of pancreatic cancer. In addition, the risk was significant among patients with increasing age, history of chronic pancreatitis and tobacco use. Patients with chronic pancreatitis and T2DM with the adjusted HR was 12.12 (95% Cl: 6.02, 24.40), they were 12 times more likely to develop pancreatic cancer. The effect of T2DM and chronic pancreatitis on pancreatic cancer risk was at least additive after adjusting for known risk factors. Incidence was highest in patients with more than 5 year duration of type 2 diabetes.
Risk minimisation measures	None; Routine pharmacovigilance only

Table I.B.2.3: Missing Information: Exposure during pregnancy and lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Fertility, pregnancy, and lactation

I.B.3 Post-Authorisation Development Plan

I.B.3.1 Studies Which are Conditions of the Marketing Authorisation

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

I.B.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Ristfor.