Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for INCRESYNC

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

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

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

I. The medicine and what it is used for

INCRESYNC is authorised for second- or third-line treatment in adult patients aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on pioglitazone alone, and for whom metformin is inappropriate due to contraindications or Intolerance (see SmPC for the full indication). It contains ALOGLIPTIN/ PIOGLITAZONE as the active substance and it is taken by mouth as a tablet.

Further information about the evaluation of INCRESYNC's benefits can be found in INCRESYNC'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/incresync

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of INCRESYNC, together with measures to minimise such risks and the proposed studies for learning more about INCRESYNC'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.

II.A List of Important Risks and Missing Information

Important risks of INCRESYNC 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 INCRESYNC. 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	None
Important Potential Risks	Pancreatic cancer (alogliptin)
Missing Information	Use during pregnancy and lactation (alogliptin)

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk Pancreatic cancer (alogliptin)	
Evidence for Linking the Risk to the Medicine	A publication by a group of academic researchers has raised concerns of an increased risk of pancreatitis and cellular changes in patients treated T2DM with GLP-1 based therapies and DPP-4 inhibitors. In March 2013, the CHMP were requested in consultation with the PRAC to give an opinion under Article 5(3) of Regulation (EC) 726/2004, regarding this recently published data, to determine its potential impact on the centrally-authorized GLP-1 agonists and DPP-4 inhibitor products, considering other data already available. This procedure is completed on 25 July 2013. On this basis pancreatic cancer has been included as a potential risk for alogliptin at the request of the CHMP.
Risk Factors and Risk Groups	There are known risk factors associated with development of pancreatic cancer; among these are gender (men are 30% more at risk), age (70% are age 65 years or older), race (African-Americans are at higher risk, possibly due to smoking, obesity and diabetes), smoking (responsible for 20%-30% of pancreatic cancers), obesity, diabetes, chronic pancreatitis, liver cirrhosis, family history, occupational exposure to pesticides, dyes, chemicals used in metal refining, and genetic syndromes, such as mutations in genes such as BRCA2, p16/CDKN2A (familial melanoma), and PRSSi (familial pancreatitis), Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), Peutz-Jeghers syndrome, von Hippel-Lindau syndrome, neurofibromatosis type 1 (gene mutation), and multiple endocrine neoplasia type 1.
Risk Minimisation Measures	**Routine risk minimization measures:** Targeted Malignancy Follow-up Form for Alogliptin for Pancreatic cancer AEs

	Additional risk minimization measures: Not applicable.

Missing Information Use during pregnancy and lactation (alogliptin)	
Risk Minimisation Measures	**Routine risk minimization measures:** SmPC sections 4.4, 4.6, 5.3 and PL section 2 **Additional risk minimization measures:** None required

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 INCRESYNC.

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

There are no studies required for INCRESYNC.