# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

## I. Summary of the Risk Management Plan for Xelevia

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

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

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

## I.A The Medicine and What It Is Used For

Xelevia is authorised for patients with type 2 diabetes mellitus, Xelevia is indicated to improve glycemic control:

as **monotherapy**

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as **dual oral therapy** in combination with

- metformin when diet and exercise plus metformin alone do not provide adequate glycemic control.
- a sulfonylurea when diet and exercise plus maximal tolerated dose of a sulfonylurea alone do not provide adequate glycemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma PPARγ agonist (thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycemic control.

as **triple oral therapy** in combination with

- a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.

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Xelevia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycemic control.

Refer to SmPC for the full indication.

It contains sitagliptin as the active substance and it is given orally.

Further information about the evaluation of Xelevia's benefits can be found in Xelevia'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/000762/human_med_001156.jsp&mid=WC0b01ac058001d124

## I.B Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

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

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

Important risks of Xelevia 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 Xelevia. 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 | None |
| Important potential risks | Pancreatic cancer |
| Missing information | Exposure during pregnancy and lactation |

Xelevia has been marketed for 12 years since 2006 with over 55 million patient-years of treatment. The safety profile has been well-characterized 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 characterize any identified or potential risk that would alter the established risk-benefit profile for Xelevia. There are also no additional risk minimization activities planned or warranted beyond communication of the safety profile in the SmPC and the Patient Leaflet. There are no important safety concerns (important identified or potential risks) for which additional pharmacovigilance activities is to be planned.

In conclusion, continued spontaneous safety surveillance will be sufficient to monitor the safety profile and labeling will provide sufficient routine risk minimization.

## I.B.2 Summary of Important Risks

### Table I.B.2.1: 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 were no significant differences 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 |

### Table II.B.2.2: Missing Information: Exposure during pregnancy and lactation

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC: Section 4.6 Fertility, pregnancy, and lactation |

## I.B.3 Post-Authorization Development Plan

### I.B.3.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Xelevia.

### I.B.3.2 Other Studies in Post-Authorization Development Plan

There are no studies required for Xelevia.

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