SUMMARY OF RISK MANAGEMENT PLAN FOR TRAJENTA AND JENTADUETO (LINAGLIPTIN AND LINAGLIPTIN / METFORMIN)

This is a summary of the Risk Management Plan (RMP) for Trajenta and Jentadueto. The RMP details important risks of Trajenta and Jentadueto, how these risks can be minimised, and how more information will be obtained about Trajenta's and Jentadueto's risks and uncertainties (missing information).

The Summaries of Product Characteristics (SmPCs) for Trajenta and Jentadueto and their package leaflets give essential information to healthcare professionals and patients on how Trajenta and Jentadueto should be used.

This summary of the RMP for Trajenta and Jentadueto should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all of 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 the Trajenta and Jentadueto RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Trajenta and Jentadueto are authorised for Type 2 diabetes mellitus (see SmPCs for the full indications). Both medicines contain linagliptin as the active substance and in addition, Jentadueto contains metformin. Both Trajenta and Jentadueto are given orally.

Further information about the evaluation of benefits of these medicines can be found in the EPARs for Trajenta and Jentadueto, including plain-language summaries, available on the EMA website, under the medicine's webpage.

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

Important risks of Trajenta and Jentadueto, together with measures to minimise such risks and the proposed studies for learning more about their 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 the case of Trajenta and Jentadueto, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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 Trajenta or Jentadueto is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Trajenta and Jentadueto 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 Trajenta or Jentadueto. 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	Pancreatitis
Important potential risks	Pancreatic cancer
Missing information	Pregnancy/breast-feeding

II.B Summary of important risks

Table 2 Important identified risks

Pancreatitis	
Evidence for linking the risk to the medicine	In clinical trials, pancreatitis occurred more frequently in patients treated with linagliptin than in those treated with either comparators (active substances used as a reference) or placebo (dummy with no active therapeutic effect).
Risk factors and risk groups	Patients with T2DM have an increased risk for pancreatitis. Further, obesity, history of alcohol use, history of smoking, higher comorbidity index, hypertriglyceridaemia, and any history of gallbladder disease are important risk factors of acute pancreatitis (see also Section SVII.3.1.1.4). Results of a retrospective cohort study using data from 2007 to 2009 of a large US medical and pharmacy claims database also show a higher percentage of biliary stone disease and hypertriglyceridaemia among patients with diabetes compared to patients without diabetes. Biliary stone disease was diagnosed in 0.84% of the diabetics compared to 0.60% in the non-diabetics ($p<0.0001$). The respective numbers for hypertriglyceridaemia were 1.71% vs. 0.95% ($p<0.0001$).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Available by prescription only Additional risk minimisation measures: None

Table 3 Important potential risk

Pancreatic cancer	
Evidence for linking the risk to the medicine	Pancreatic cancer was added as an important potential risk at the request of the CHMP in the EMA. Recently completed CV outcome trials for DPP-4 inhibitors have shown no increase in pancreatic cancer cases in patients treated with DPP-4 inhibitors as compared to those on placebo or active comparator.
Risk factors and risk groups	Pancreatic cancer classically presents late in life, and has a poor prognosis and rapid clinical course. The risk factors are complex and work is still ongoing in identifying risk factors and their impact on the risk of developing pancreatic cancer. The current identified and potential risk factors are summarised below. *Identified risk factors for pancreatic cancer* • Smoking (in which a dose response relationship has been observed) • Obesity • Family history • Genetic factors including mutations in breast cancer 2 (BRCA2), CDKN2A gene (familial atypical multiple mole-melanoma [FAMMM] syndrome), STK11 (Peutz-Jeghers Syndrome), PRSS1 (hereditary pancreatitis), MLH1 or MSH2 (hereditary non-polyposis colorectal cancer [HNPCC] or Lynch syndrome) • Non-O blood groups (the significance of this is still unknown) • Chronic Infections, e.g. hepatitis B virus, hepatitis C virus, Helicobacter pylori • Surgery, e.g. cholecystectomy, partial gastrectomy • Pancreatitis and chronic pancreatitis (familial & tropical pancreatitis appears to show this more strongly) *Potential risk factors for pancreatic cancer (as some studies have shown a relationship and some have not, there is an unknown relationship)* • Alcohol consumption • Sunlight & vitamin D • Diabetes

Table 3 (cont'd) Important potential risk

Pancreatic cancer (cont'd)	• Consumption of red and processed meat
Risk factors and risk groups (cont'd)	• Other medical conditions that may increase risk include cystic fibrosis & periodontal disease (the cystic fibrosis gene is also associated with pancreatitis; it is not clear if this association with pancreatic cancer is due to the pancreatitis being a risk for cancer or cystic fibrosis being a risk in its own right) *Previous suspected associations, which now seem to be disregarded* • Caffeine (found to not have an association in a recent meta-analysis) Considering patients with pancreatic cancer, at diagnosis about 25% have diabetes mellitus, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels). Compared with non-diabetic individuals, patients with long-term (≥5 years) T2DM have a 50% increased risk of pancreatic cancer. Pancreatic cancer can cause diabetes, and sometimes diabetes is an early sign of the tumour so the observed data can be difficult to interpret: Do patients with diabetes have a higher risk of cancer or is this confounded by the proportion of the diabetic patients who develop pancreatic cancer whose diabetes is caused by pancreatic failure associated with the clinically undetected cancer? Elevated pancreatic cancer risk has also been reported among individuals with type-I diabetes. Recent reports also suggest that hyperglycaemia, abnormal glucose metabolism and insulin resistance are associated with increased risk of pancreatic cancer.
Risk minimisation measures	Routine risk minimisation measures: • Available by prescription only Additional risk minimisation measures: None

Table 4 Missing information

Pregnancy/breast-feeding	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Available by prescription only Additional risk minimisation measures: None

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 obligations of Trajenta or Jentadueto.

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

None

ABBREVIATIONS

CV	Cardiovascular
DPP-4	Dipeptidyl peptidase-4
EMA	European Medicines Agency
EPAR	European Public Assessment Report
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus