EU RMP Part VI

Drug Substance	Exenatide
Version Number	36
Succession Number	1

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR EXENATIDE

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR EXENATIDE

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

The Summary of Product Characteristics (SmPC) and package leaflet for BYETTA and BYDUREON (QW and QWS) give essential information to healthcare professionals and patients on how BYETTA or BYDUREON (QW and QWS) should be used.

This summary of the RMP for BYETTA and BYDUREON (QW and QWS) 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 the RMP for BYETTA and BYDUREON (QW and QWS).

THE MEDICINE AND WHAT IT IS USED FOR

BYETTA is indicated for treatment of T2DM in combination with:

- Metformin
- SU
- TZDs
- Metformin and an SU
- Metformin and a TZD

In adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents (see the SmPC for the full indication).

BYDUREON (QW and QWS) is indicated in patients 10 years and older and adults with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products, including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see the SmPC for the full indication).

BYETTA and BYDUREON (QW and QWS) are medications that contain exenatide as the active substance and it is given as a subcutaneous injection.

Further information on the evaluation of the benefits of BYETTA and BYDUREON (QW and QWS) can be found in the EPAR on these drugs, including in the plain-language summary, available on the EMA website, under the medicine's webpage for

BYETTA: https://www.ema.europa.eu/en/medicines/human/EPAR/byetta

BYDUREON: https://www.ema.europa.eu/en/medicines/human/EPAR/bydureon

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

Important risks of BYETTA and BYDUREON (QW and QWS), together with measures to minimise such risks and the proposed studies for learning more about the risks associated with BYETTA and BYDUREON (QW and QWS) 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 (eg, 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 Periodic Benefit-Risk Evaluation Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

List of Important Risks and Missing Information

Important risks of BYETTA and BYDUREON (QW and QWS) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 BYETTA or BYDUREON (QW and QWS). 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 (eg, on the long-term use of the medicine).

Summary of Safety Concerns

Important identified risks	None
Important potential risks	Pancreatic cancer Thyroid neoplasms

Summary of Important Risks

Important Potential Risk: Pancreatic Cancer

Evidence for linking the risk to the medicine	The FDA and EMA have independently evaluated the pancreatic safety of incretin-based drugs and published a joint assessment in the New England Journal of Medicine. It was concluded that while both agencies continue to investigate the safety signal, "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed in the scientific literature and in the media, are inconsistent with the current data" (Egan et al 2014). In the exenatide clinical programme (including the EXSCEL study), no evidence of an increased risk of pancreatic cancer was seen.
Risk factors and risk groups	Age, gender, race, cigarette smoking, obesity, diabetes, chronic pancreatitis, cirrhosis of the liver, occupational exposure, family history, infection of the stomach with the ulcer-causing bacteria *Helicobacter pylori*.
Risk minimisation measures	Routine risk minimisation measures: None No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A Pan-European Post-Authorisation Safety Study to: (1) estimate the IR and HR for pancreatic cancer associated with exposure to any exenatide formulation (BYETTA or BYDUREON/BYDUREON BCise), compared with exposure to non-GLP-1 RA-based GLDs, among patients with T2DM. (2) estimate the IR and HR for pancreatic cancer associated with exposure to exenatide once weekly formulation (BYDUREON/ BYDUREON BCise) compared with exposure to non-GLP-1 RA-based GLDs, among patients with T2DM

FDA, Food and Drug Administration; EMA, European Medicines Agency; GLD, glucose-lowering drugs; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; IR, incidence rate; T2DM, type 2 diabetes mellitus.

Important Potential Risk: Thyroid Neoplasms

Evidence for linking the risk to the medicine	In the nonclinical programme with exenatide QW, thyroid C-cell hyperplasia and neoplasia were observed at all exenatide QW dose levels in a rat carcinogenicity study.

Important Potential Risk: Thyroid Neoplasms

Risk factors and risk groups	Gender, age, race, genetics, radiation exposure, diet low in iodine.
Risk minimisation measures	Routine risk minimisation measures: None No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: D5551R00001 A registry of incident cases of medullary thyroid carcinoma in adults in the US to characterise their medical histories and possible risk factors, including history of treatment with exenatide QW and other long-acting GLP-1 RAs.

GLP-1 RAs, glucagon-like peptide-1 receptor agonists; QW, once weekly; US, United States.

Post-Authorisation Development Plan

Studies Which Are Conditions of the Marketing Authorisation

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

Other Studies in Post-Authorisation Development Plan

D5551R00015

Study short name and title: EXCEED - A Pan-European Post-Authorisation Safety Study: Risk of Pancreatic Cancer Among Type 2 Diabetes Patients who Initiated Exenatide as Compared with those who Initiated Other non-Glucagon-Like Peptide 1 Receptor Agonists-based Glucose Lowering Drugs

Purpose of the study: (1) To estimate the IR and HR for pancreatic cancer associated with exposure to any exenatide formulation (BYETTA or BYDUREON/BYDUREON BCise), compared with exposure to non-GLP-1 RA-based GLDs, among patients with T2DM. (2) To estimate the IR and HR for pancreatic cancer associated with exposure to exenatide once-weekly formulation (BYDUREON/ BYDUREON BCise) compared with exposure to non-GLP-1 RA-based GLDs, among patients with T2DM.

D5551R00001

Study short name and title: Medullary Thyroid Carcinoma (MTC) Surveillance Study: A Case Series Registry.

Purpose of the study: To establish a multicentre registry of incident cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with exenatide QW and other long-acting GLP-1 RAs.