Trulicity®

(dulaglutide)

0.75 mg / 1.5 mg / 3 mg / 4.5 mg, solution for injection

Summary of Risk Management Plan (RMP)

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Based on EU-RMP Version 4.2

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Trulicity is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Trulicity in Switzerland is the „Arzneimittelinformation/ Information sur le médicament“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Trulicity.

I - The Medicine and What It Is Used for

Trulicity is authorised for T2DM (see SmPC for the full indication). It contains dulaglutide as the active substance and it is given by injection.

Further information about the evaluation of Trulicity's benefits can be found in Trulicity'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/trulicity#overview-section

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Trulicity, together with measures to minimise such risks and the proposed studies for learning more about Trulicity's risks, are outlined as follows.

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. Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions, including PSUR assessment, is collected continuously and analysed regularly 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 Trulicity is not yet available, it is listed under 'missing information' as follows.

II.A List of Important Risks and Missing Information

Important risks of Trulicity 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 Trulicity. 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.

List of Important Risks and Missing Information	
Important Identified Risks	• Acute pancreatitis • Gastrointestinal events • Hypersensitivity, including anaphylactic reaction
Important Potential Risks	• Thyroid C-cell tumours • Pancreatic malignancy • Medication errors (more than 1 injection per week)
Missing Information	• Use in pregnant and/or breastfeeding women • Use in patients with congestive heart failure

II.B Summary of Important Risks

Important Identified Risk: Acute pancreatitis	
Evidence for linking the risk to the medicine	Pancreatitis has been described with the use of GLP-1 RAs, including dulaglutide. There have been many studies exploring a potential causal association of pancreatitis with the use of medicinal products like dulaglutide, but the conclusions of these studies have been inconsistent. Some reports indicate a causal association of these agents with pancreatitis, while others have failed to identify such an association. Interpretation of these reports is complicated by the fact that patients with T2DM have a higher risk of pancreatitis than the general population. A joint FDA and EMA publication states that data demonstrate conflicting opinions about the strength of the association (Egan et al. 2014). To date, no causal relationship between dulaglutide and acute pancreatitis has been established. From the dulaglutide clinical trial programme, similar numbers of cases have been reported with placebo treatment as with dulaglutide treatment. Most cases are confounded, if not by T2DM itself, then by gallstones, alcohol abuse, or increased lipids.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU • H9X-MC-B013: Dulaglutide Retrospective Study See Section II.C of this summary for an overview of the postauthorisation development plan.

Summary of Important Risks

Important Identified Risk: Gastrointestinal events	
Evidence for linking the risk to the medicine	Gastrointestinal events such as nausea, vomiting, and diarrhoea are frequent, occur more often with dulaglutide than with placebo, and are dose related. As with other agents in the class, these GI events are well characterised and are listed as adverse drug reactions.
Risk factors and risk groups	None identified.
Risk minimisation measures	• SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009) See Section II.C of this summary for an overview of the postauthorisation development plan.
Important Identified Risk: Hypersensitivity, including anaphylactic reaction	
Evidence for linking the risk to the medicine	The overall weight of evidence linking dulaglutide exposure to significant and clinically concerning hypersensitivity reactions sufficient to warrant this being an important risk is very low. Although hypersensitivity and anaphylactic reactions are listed as uncommon and rare ADRs for dulaglutide, evidence from available clinical trial and spontaneous reporting data sources indicate that the safety profile has not changed since dulaglutide was first approved in 2014.
Risk factors and risk groups	No specific patient group at risk or risk factors could be identified for dulaglutide.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009) See Section II.C of this summary for an overview of the postauthorisation development plan.

Summary of Important Risks

Important Potential Risk: Thyroid C-cell tumours	
Evidence for linking the risk to the medicine	The only evidence for this potential risk comes from rodents (rats only in the case of dulaglutide) with near lifetime exposure. This effect on rodent thyroids has been observed consistently with other long-acting GLP-1 RAs like dulaglutide. The relevance to humans cannot be determined from clinical and nonclinical studies. At this time, there is insufficient evidence to attribute thyroid C-cell disease to dulaglutide. As cancer can take many years to develop, the database for dulaglutide is of insufficient size and exposure duration to assess the relevance of these findings in rats to dulaglutide use in patients.
Risk factors and risk groups	Compared to the general population, patients with diabetes have a higher prevalence of thyroid disorders (6.6% vs 10.8%). However, the link between T2DM and thyroid cancer is arguable. Some studies did not show an association between diabetes, including T2DM, and thyroid cancer risk, while other studies showed that patients with diabetes are 20% to 34% more likely to develop thyroid cancer than those without diabetes. As a result, no specific risk factors in relation to dulaglutide use have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B001: Medullary Thyroid Carcinoma (MTC) Surveillance Study • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU • H9X-MC-B013: Dulaglutide Retrospective Study See Section II.C of this summary for an overview of the postauthorisation development plan.

Summary of Important Risks

Important Potential Risk: Pancreatic malignancy	
Evidence for linking the risk to the medicine	There has been some concern that GLP-1 RA–mediated insulin secretion could promote tumour formation, including pancreatic malignancies. Some reports indicate a causal association with these agents, while others have failed to show such an association. A joint FDA and EMA publication states that data demonstrate conflicting opinions about the strength of the association. To date, no causal relationship between dulaglutide and pancreatic malignancy has been established. From the clinical trial programme for dulaglutide, only a few cases of pancreatic malignancy were reported, with short exposure and time to diagnosis.
Risk factors and risk groups	Except for the excess risk of pancreatic malignancy and pancreatitis associated with T2DM, no risk factors specific to dulaglutide treatment have been identified.
Risk minimisation measures	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU • H9X-MC-B013: Dulaglutide Retrospective Study See Section II.C of this summary for an overview of the postauthorisation development plan.

Summary of Important Risks

Important Potential Risk: Medication errors (more than 1 injection per week)	
Evidence for linking the risk to the medicine	There is very limited evidence that 'medication errors' is a significant issue with dulaglutide based on current data. It was added to the EU RMP when dulaglutide was authorised in the EU at the request of the regulators, as there was a concern that patients could administer more than 1 injection of dulaglutide per week when switching from a twice-weekly injection of another T2DM medication to dulaglutide (an injection taken once a week). Based on limited clinical trial data at that time, no serious outcomes had been reported.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • PL Section 3 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU See Section II.C of this summary for an overview of the postauthorisation development plan.

Summary of Important Risks

Missing Information: Use in pregnant and/or breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU See Section II.C of this summary for an overview of the postauthorisation development plan.
Missing Information: Use in patients with congestive heart failure	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • H9X-MC-B009: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU See Section II.C of this summary for an overview of the postauthorisation development plan.

Abbreviations: EMA = European Medicines Agency; EU = European Union; FDA = US Food and Drug Administration; GLP-1 = glucagon-like peptide 1; PL = package leaflet; RA = receptor agonist; RMP = risk management plan; SmPC = summary of product characteristics; T2DM = type 2 diabetes mellitus.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of dulaglutide.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: Medullary Thyroid Carcinoma (MTC) Surveillance Study (H9X-MC-B001)

Purpose of the study: This is a prospective registry conducted through state cancer registries to determine the annual incidence of MTC in the United States and to identify any possible increase related to the introduction of long-acting GLP-1 RAs, including dulaglutide, into the US market. This study addresses the important potential risk of MTC observed in rodents across all GLP-1 agonists.

Study short name: Dulaglutide Modified-Prescription-Event Monitoring and Network Database Study in the EU (H9X-MC-B009)

Purpose of the study: This study will monitor the occurrences of events of interest and ensure that the profile and rate remain consistent with what has been seen in clinical trials. This study will address the following safety concerns:

- Acute pancreatitis
- Hypersensitivity
- Pancreatic and thyroid cancers
- CV events, including heart rate (tachycardia) and conduction abnormalities (AV block)
- GI effects/gastric stenosis
- Medication errors

The above outcomes will also be described in the dulaglutide subpopulations identified as missing information.

Study short name: Dulaglutide Retrospective Study (H9X-MC-B013)
Purpose of the study: This study will estimate the incidence rates of events of interest among patients with T2DM treated with dulaglutide compared to other GLP-1 RAs. It will address the safety concerns of pancreatitis and pancreatic and thyroid cancers.