Summary of risk management plan for LANTUS/TOUJEO (formerly OPTISULIN) (Insulin Glargine)

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

LANTUS/TOUJEO (formerly OPTISULIN) summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how LANTUS/TOUJEO (formerly OPTISULIN) should be used.

This summary of the RMP for LANTUS/TOUJEO (formerly OPTISULIN) 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 LANTUS/TOUJEO (formerly OPTISULIN) RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Insulin glargine 100 U/mL (LANTUS) is authorized for treatment of diabetes mellitus in adults, adolescents and children aged 2 years or above.

Insulin glargine 300 U/mL (TOUJEO) is authorized for treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years (see SmPC for the full indication). It contains Insulin Glargine as the active substance and it is given by subcutaneously.

Further information about the evaluation of LANTUS/TOUJEO (formerly OPTISULIN) benefits can be found in LANTUS/TOUJEO (formerly OPTISULIN) EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

LANTUS EPAR: https://www.ema.europa.eu/en/documents/overview/lantus-epar-summary-public_en.pdf

TOUJEO EPAR: https://www.ema.europa.eu/en/documents/overview/toujeo-epar-medicine-overview_en.pdf

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of LANTUS/TOUJEO (formerly OPTISULIN), together with measures to minimize such risks and the proposed studies for learning more about LANTUS/TOUJEO (formerly OPTISULIN) risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of LANTUS/TOUJEO (formerly OPTISULIN), these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (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 LANTUS/TOUJEO (formerly OPTISULIN) is not yet available, it is listed under 'missing information' outlined in the next section.

II.A List of important risks and missing information

Important risks of LANTUS/TOUJEO (formerly OPTISULIN) are risks that need special risk management activities to further investigate or minimize 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 LANTUS/TOUJEO (formerly OPTISULIN). 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).

Table 1 - List of important risks and missing information

Important identified risk	Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins
Important potential risks	Malignancies
	Medication errors: • Mix-up between long-acting 100 U/mL and 300 U/mL strength insulin products • Unnecessary dose or unit recalculation • Switching patients between standard 100 U/mL and 300 U/mL strength insulin products without dose adjustment
Missing information	Use in pregnancy (U300 only)

II.B Summary of important risks

Table 2 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins

Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	
Evidence for linking the risk to the medicine	Postmarketing data; The Human factors Validation study showed that no mix-up between TOUJEO and other insulins occurred.
Risk factors and risk groups	Visually impaired or color blind patients without help of a person trained for the use of the device.
Risk minimization measures	**Routine risk minimization measures:** U100 SmPC: Labeled in sections 4.4 and 6.6. PL: Labeled in section 3. IFU: Step 1 U300 SmPC: Labeled in sections 4.4 and 6.6. PL: Labeled in sections 2 and 3. IFU: "Learn to inject" and Step 1-A. To enhance differentiation (not only in countries where U100 vial and syringe are marketed) a different trade name is a way to prevent patient medication error or dispensing errors. The trade name for U300 Insulin glargine is TOUJEO (TOUJEO SoloStar for the small size pen, and TOUJEO DoubleStar for the large size pen), while LANTUS is used for U100. Medicinal product subject to medical prescription. Packaging (outer carton + label). Each strength and presentation has specific pen design and color, pen label, and outer pack specific color. **Additional risk minimization measures:** None

e-CTD: Electronic Common Technical Document; IFU: Instructions For Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 3 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Malignancies

Malignancies	
Evidence for linking the risk to the medicine	Literature, clinical data.
Risk factors and risk groups	A recently published quartet of observational studies [a, b, c] assessing whether different types of insulin confer different cancer risk were considered inconsistent and inconclusive with regard to specific insulin types, but consistent with the hypothesis that insulin therapy confers increased risk. In an accompanying editorial in the same journal issue, the commissioners of these studies commented that the available evidence points to the possibility that insulin in general, or different types of insulin, may be mitogenic, that is, they enhance growth and proliferation of neoplastic cells already present, rather than being mutagenic, that is, rather than causing the de novo appearance of

Malignancies	
	malignancy in healthy tissue. Hence the evidence for increased risk appears confined to older patients with T2DM with occult foci of malignancy. Epidemiology data on the risk of cancer in the children population are provided in RMP Part II SI.
Risk minimization measures	**Routine risk minimization measures:** SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None

a Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319-28

b Habel LA, Danforth KN, Quesenberry CP, Capra A, Van Den Eeden SK, Weiss NS, et al. Cohort study of insulin glargine and risk of breast, prostate, and colorectal cancer among patients with diabetes. Diabetes Care 2013;36(12):3953-60.

c Pollak M, Russell-Jones D. Insulin analogues and cancer risk: cause for concern or cause celebre? Int J Clin Pract. 2010;64(5):628-36.

IFU: Instructions for Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics; T2DM: Type 2 Diabetes Mellitus.

Table 4 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance: Medication errors

Table 4a - Mix-up between long-acting 100 U/mL and 300 U/mL strength insulin products

Mix-up between long-acting 100 U/mL and 300 U/mL strength insulin products	
Evidence for linking the risk to the medicine	The Human factors Validation study showed that no mix-up between TOUJEO and other insulins occurred.
Risk factors and risk groups	Visually impaired or color blind patients without help of a person trained for the use of the device.
Risk minimization measures	**Routine risk minimization measures:** <u>U100</u> SmPC: Labeled in sections 4.4 and 6.6. PL: Labeled in section 3. IFU: Step 1-A. Trade names are different. Packaging mentions the strength. Pack, pen and labels have different color and design. Medicinal product subject to medical prescription except during switch period, patients should not own products with different concentrations. <u>U300</u> SmPC: Labeled in sections 4.4 and 6.6. PL: Labeled in sections 2 and 3. IFU: “Learn to inject” and Step 1-A. Trade names are different. Packaging mentions the strength.

	Pack and pen have different color and design. Medicinal product subject to medical prescription. Except during switch period, patients should not own products with different concentrations. **Additional risk minimization measures:** None

e-CTD: Electronic-Common Technical Document; IFU: Instructions For Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 4b - Unnecessary dose or unit recalculation

Unnecessary dose or unit recalculation	
Evidence for linking the risk to the medicine	The postmarketing experience with LANTUS: A cumulative search of the pharmacovigilance database through 20-Jan-2023 was performed for all solicited (related and unrelated) and unsolicited cases (including both diagnoses and symptoms). The review of the postmarketing pharmacovigilance databases for medication errors due to "unnecessary re-calculation of the units needed" revealed 19 cases. Human Factors study conducted in US confirmed the possibility of mistakes.
Risk factors and risk groups	Could impact the prescribers or patients if not familiar with the instructions for use.
Risk minimization measures	**Routine risk minimization measures:** U100 SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. U300 SmPC: Labeled in section 4.2. PL: Labeled in section 3. IFU: Step 4 Medicinal product subject to medical prescription. The dose window of the pen shows the dose in units. **Additional risk minimization measures:** HCP educational material: HCP brochure Patient educational material: Patient brochure to patients treated with TOUJEO SoloStar/DoubleStar

HCP: Healthcare Professional; IFU: Instructions For Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics; US: United States.

Table 4c - Medication error associated with Switching patients between standard 100 U/mL and 300 U/mL strength insulin products without dose adjustment

Switching patients between standard 100 U/mL and 300 U/mL strength insulin products without dose adjustment	
Evidence for linking the risk to the medicine	The postmarketing experience with LANTUS: Not applicable.

Risk factors and risk groups	Not applicable
Risk minimization measures	**Routine risk minimization measures:** U100 SmPC: Labeled in section 4.2. PL: None IFU: None Medicinal product subject to medical prescription. U300 SmPC: Labeled in sections 4.2 and 4.4. PL: Labeled in sections 2 and 3. IFU: Step 1-A Medicinal product subject to medical prescription. **Additional risk minimization measures:** HCP educational material: HCP brochure. Patient educational material: Patient brochure to patients treated with TOUJEO SoloStar/DoubleStar.

IFU: Instructions For Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

e-CTD: Electronic-Common Technical Document; HCP: Healthcare Professional; IFU: Instructions For Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics; US: United States.

Table 5 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in pregnancy (U300 only)

Use in pregnancy (U300 only)	
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in section 4.6. PL: Labeled in section 2. IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None

IFU: Instructions for Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.I Studies which are conditions of the marketing authorization.

None

II.C.II Other studies in post-authorization development plan

None