WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	**Insulin Glargine Impact**[1]
Manufacturer of Prequalified Product:	Sanofi-Aventis Deutschland GmbH (LOC-100000869) Brüningstraße 50 Höchst 65926 Frankfurt am Main
Active Pharmaceutical Ingredient (API):	Insulin Glargine
Pharmaco-therapeutic group (ATC Codes):	A10AE04 (insulin glargine)
WHO recommended therapeutic indication:	Diabetes mellitus

1 Introduction

Insulin Glargine Impact (insulin glargine) is an insulin analogue with a prolonged duration of action after subcutaneous injection, produced by recombinant DNA technology using Escherichia coli (K12 strains).

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely "European Medicines Agency" (https://www.ema.europa.eu/en) in line with the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

[2] https://extranet.who.int/pqweb/sites/default/files/documents/03_GLs_Submission_SBP_Pilot_AbridgedPathway_insulinFeb2020.pdf

2 Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant provided performance qualification testing of the product's transport by air and sea freight performed in 3 separate shipments. Duration of the air freight was 16 days while duration of air freight was 1 day. The temperature had to be maintained between +2°C and +8°C and monitored according to applicable procedures. These studies provided evidence that the products are maintained at required temperature during transportation.

Furthermore, the Applicant also provided stability studies to assess the quality of the product during different shipment conditions. In each shipment the storage temperature was monitored, and the chemical and physical stability of the product examined. The shipping pallets were loaded considering the worst-case position for the samples to be analyzed.

Finally, the applicant also provided evidence that the transport of product is performed according to GDP requirements and according to WHO Technical Report Series, No. 961, 2011, Annex 9.

The shipments are continuously monitored by calibrated temperature logging devices from the moment the pallets are dispatched until they are received at their final destination. Furthermore, data from the temperature loggers are evaluated before release. Any deviations from the allowed temperatures will be handled in a deviation report according to applicant's procedures.

Arrangements for handling complaints and product recalls

The applicant provided information on the procedure for the identification, handling and management of product complaint, identification, handling of critical product complains including decisions, requirement and process for information to authorities and handling of product recalls.

The Applicant submitted the procedure for the management of products complaints. The procedure applies to all products quality complaints for the Applicant. The procedure also describes the review of complaints and trends data that lead to corrective and preventive measures.

The procedure applies to all product complaints concerning products marketed by the applicant, regardless of their origin, and to products handled by third parties as a Market Authorization Holder on behalf of the applicant, but also on the suspected counterfeit or falsified products. The procedure also applies to subcontractors involved in such activities.

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the product defects/serious quality issues definition, investigation process and risk assessment, process of recalls, established timelines for recall notification to National Medicines Regulatory Authorities, recall arrangements and actions to put in place at the distribution level as well as description of the annual mock-recall. The applicant confirms that handling of complaints and recalls are clearly defined and part of the template agreements or contracts between manufacturer and relevant third parties.

Stability of the product

Unopened vials: Store in a refrigerator (2°C-8°C).

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the vial in the outer carton in order to protect from light.

Shelf-life after first use of Vial – Once in use, vials may be stored for a maximum of 4 weeks not above 30°C and away from direct heat or direct light. Keep the vials in the outer carton in order to protect from light.

Conclusion: The quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: The pharmacovigilance part of the dossier is accepted.

[3] https://extranet.who.int/pqweb/sites/default/files/documents/RMP_AddStructureDec2019-2.pdf

Risk Management Plan Addendum for WHO Pre-Qualification

Insulin Glargine 100 U/mL solution for injection

Data Lock Point (DLP{ XE " DLP " \f Abbreviation \t "Data Lock Point" **})**	**01-Nov-2022**
{ XE " RMP " \f Abbreviation \t "Risk Management Plan" **}Version number**	**Version 1.1**
Date	**20-Jan-2023**

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1. GENERAL INFORMATION

This addendum to the Sanofi insulin glargine risk management plan (RMP) supports the WHO pre-qualification (WHO PQ) application for Sanofi product: Insulin Glargine 100 U/mL solution for injection.

Insulin glargine is an insulin analogue with a prolonged duration of action after subcutaneous injection, produced by recombinant DNA technology using Escherichia coli (K12 strains). It is approved for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years or above.

Sanofi acknowledges that healthcare settings and infrastructure may vary between countries, and continuously evaluates the adequacy of the safety concerns via routine pharmacovigilance (PV), and traceability of the product at a national level.

Table 1 - Product Overview

Active substance(s) (INN or common name)	Insulin glargine
Pharmacotherapeutic group(s) (ATC Code)	A10AE04 Anatomical main group: Alimentary tract and metabolism. Therapeutic subgroup: Drugs used in diabetes. Pharmacological subgroup: Insulins and analogues. Chemical subgroup: Insulins and analogues for injection, long-acting.
Marketing Authorization Holder or Applicant	Sanofi-Aventis Deutschland GmbH
Medicinal products to which this RMP refers	Insulin glargine 100 U/mL solution for injection
Invented name(s)	LANTUS / Insulin Glargine Impact
Brief description of the product	Important information about its composition Insulin glargine, the active ingredient in LANTUS, is an insulin analogue with a prolonged duration of action after subcutaneous injection, produced by recombinant DNA technology using *Escherichia coli* (K12 strains).
	Summary of mode action The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.
	Chemical class Structural modifications (C-terminal elongation of the B chain by two arginines and replacement of the C-terminal amino acid of the A-chain by glycine) shift the isoelectric point towards neutral pH. This results in a delay in dissociation of the hexamer complexes into monomers after subcutaneous injection, and a prolonged absorption from the injection site.

Indication(s)	Insulin glargine 100 U/mL: Treatment of diabetes mellitus in adults, adolescents and children aged 2 years or above.
Dosage	Insulin glargine 100 U/mL is to be administered subcutaneously once daily at any time but at the same time each day. The dose regimen (dose and timing) should be individually adjusted.
Pharmaceutical form(s) and strength(s)	Solution for injection, 100 U/mL (in vial, cartridges and disposable [pre-filled] pen SoloStar).
First marketing authorization	20 April 2000
Years of post-marketing experience	>22 years
ATC**{** XE " ATC " \f Abbreviation \t "Anatomical Therapeutic Chemical" **}**: Anatomical Therapeutic Chemical; eCTD**{** XE " eCTD " \f Abbreviation \t "Electronic Common Technical Document" **}**: Electronic Common Technical Document; DNA**{** XE " DNA " \f Abbreviation \t "Deoxyribonucleic Acid" **}**: Deoxyribonucleic Acid; EEA**{** XE " EEA " \f Abbreviation \t "European Economic Area" **}**: European Economic Area; EMEA**{** XE " EMEA " \f Abbreviation \t "European Medicines Agency" **}**: European Medicines Agency; EU**{** XE " EU " \f Abbreviation \t "European Union" **}**: European Union; INN: International Nonproprietary Name; RMP: Risk Management Plan.	

2. SAFETY CONCERNS

For global harmonization, safety concerns about Insulin Glargine 100 U/mL solution for injection for WHO PQ are aligned with those included in the latest approved version 6.1 of the EU RMP for Lantus®. In addition, local specific condition can be considerable and the local specific RMP could address to those at national level to ensure upon request of regulatory authorities. The applicant will assess the local healthcare settings and practice, infrastructure, epidemiology in the area where the product will be newly marketed, in comparison to the EU setting. It will contribute to identify any potential safety concerns which are newly arisen depending on the local specific condition.

Table 2 - List of safety concerns

Important identified risks	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 units/mL and 300 units/mL strength insulin products • Unnecessary dose or unit recalculation • Switching patients between standard 100 units/mL and 300 units/mL strength insulin products without dose adjustment
Missing information	None

3. PHARMACOVIGILANCE ACTIVITIES

Sanofi's global pharmacovigilance (GPV) organization is split into Global sites and Country sites. The country sites are organized by regions managed by Regional Safety Head. In the countries' network, the local PV responsible person is responsible for ensuring that the local PV system is in place including the monitoring of local PV legislation of the country(ies) under his/her responsibility and for keeping Global team informed on the current national requirements. No additional PV activities are currently deemed necessary on a national level for Sanofi's Insulin Glargine 100 U/mL solution for injection.

The organization design in place within GPV and with its business partners ensures that the Chief Safety Officer (CSO), the QPPV, GPV unit Heads and the Chief Medical Officer (CMO) via delegation to the CSO have a full oversight over the PV system.

The CSO, who is also the GPV Head, is responsible for ensuring that sufficient pharmacovigilance related resources, quality systems/procedures and tools/training are implemented within GPV. The position of the QPPV, in having a direct reporting line to the CSO, guarantees that the qualified person has sufficient authority over the PV system in order to promote, maintain and improve regulatory compliance.

Current monitoring is performed by means of quarterly signal detection and through the global periodic safety update reports (PSURs/PBRERs). Signal detection involves the examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources to detect new risks or changes to existing risks of a product. Any new safety concern that may arise is followed up with appropriate actions such as introduction of new risk minimization measures, if needed.

Additionally, signals validated by Sanofi are presented in detail in PSURs/PBRERs. The routine PSURs/PBRERs will be prepared in accordance with the national requirements for submission to the national health authorities in these countries.

The requirement of any additional PV activities will be assessed through routine surveillance, factoring in the local specificities such as epidemiology, healthcare infrastructure, clinical practice and other factors. Only routine risk minimization measures in the form of the summary of product characteristics (SmPC) and the corresponding product leaflets (PLs) are presently implemented. The distribution of the SmPCs and PLs for Insulin Glargine 100 U/mL is in accordance with all national requirements. Effectiveness of risk minimization measures is assessed through routine pharmacovigilance activities.

There is a continuous monitoring of the safety profile and related benefit-risk balance of the Company portfolio from developmental through all subsequent life cycle management phases. Appropriate and diligent communication to the regulatory bodies is governed by procedures in place.

4. RISK MINIMISATION MEASURES

A well-characterized safety profile has emerged for Insulin Glargine 100 U/mL from an extensive worldwide array of safety data encompassing more than 22 years of post-marketing experience, based on worldwide safety data from more than 130 countries. Consistent with a safety profile of this level of maturity, all important risks for insulin glargine are appropriately managed, without the requirement for further risk management as of the current EMA-endorsed RMP (Version 6.1; procedure numbers EMEA/H/C/000309/II/0108).

Specifically, only routine risk minimization measures in the form of the guidance contained in the summary of product characteristics (SmPC) and the corresponding product leaflets (PLs) are presently incorporated globally into standard clinical practice relating to Insulin Glargine 100 U/mL. No additional risk minimization measures (including non-promotional educational materials, etc.) are presently active in any country for any risks, including the important identified and potential risks specified in Table 3. As there has been a lengthy presence on the global market and an extensive exposure, spread over numerous countries, to the appropriate patient populations for Insulin Glargine 100 U/mL, there is a high degree of knowledge amongst health care professionals (HCPs) in all marketed countries in relation to the safety concerns associated with the use of this insulin glargine. The distribution of the corresponding SmPCs and PLs for Insulin Glargine 100 U/mL is in accordance with all national requirements, with additional access to SmPCs, and related product information available online. Effectiveness of risk minimization measures is assessed through routine pharmacovigilance activities. In connection with any new applications for marketing authorizations in any additional countries or with any updates or other conditions for the products that should require non-promotional educational materials, such educational materials will be provided in accordance with national requirements.

Table 3 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	**Routine risk minimization measures:** SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled in section 3. IFU: Step 1 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risks		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignancies	**Routine risk minimization measures:** SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Medication errors		
• Mix-up between long-acting 100 units/mL and 300 units/mL strength insulin products	**Routine risk minimization measures:** SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled 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. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
• Unnecessary dose or unit recalculation	**Routine risk minimization measures:** SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
• Switching patients between standard 100 units/mL and 300 units/mL strength insulin products without dose adjustment	**Routine risk minimization measures:** SmPC: Labelled in section 4.2. PL: None IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
None	Not Applicable	Not Applicable

Safety concern	Risk minimization measures	Pharmacovigilance activities

HCP: Healthcare Professional; ICSR{ XE "ICSR" \f Abbreviation \t "Individual Case Safety Report" }: Individual Case Safety Report; IFU: Instructions for Use; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

5. PRODUCT TRACEABILITY

Sanofi has adequate global batch tracing systems in place to enable a clear overview of batch linkages within and outside Sanofi. Identification of any particular batch of product can be facilitated through this system. Specifically, where appropriate and possible, batch numbers from product labels are collected in association with adverse event reporting.

The essential information presented in the packaging material are provided in Annex III of the approved Insulin Glargine 100 U/mL solution for injection (Lantus®) EU SmPC.

6. SUMMARY

Insulin Glargine 100 U/mL solution for injection have well characterized safety profile, informed by more than 22 years of post-marketing experience from extensive worldwide sources. Consequently, all risks in the RMP for insulin glargine are appropriately managed by routine pharmacovigilance activities, with no requirement for additional risk minimization measures.

In summary, Sanofi considers the benefit risk balance of Insulin Glargine 100 U/mL in the approved condition of use remains favorable.