EU Risk Management Plan (Version 13.1)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

Document ID: VV-PVG-103779

EU Risk Management Plan (RMP) for insulin lispro (Humalog® and Lyumjev®)

RMP version to be assessed as part of the application: Version 13.1

Data lock point for this RMP: 16 July 2021 for CT exposure; 30 September 2021 for PM exposure

Date of final sign off: See Cover Page of this document

Rationale for submitting an updated RMP: Removal of "Severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application", which is listed as an important potential risk for the Tempo Pen and all associated risk minimisation measures. This is as a result of the PRAC assessment of the F3Z-MC-B030 PASS protocol and a request for a type IB variation to remove this important potential risk.

Summary of significant changes in this RMP:

A summary of changes to the Core RMP over time can be found in Annex 8.

Other RMP versions under evaluation

RMP version number: 11.1

Submitted on: 17 June 2021

Procedure number: EMEA/H/C/5037/X/10

Summary of evaluation: Version 11.1 of the RMP was submitted to PRAC on 25 May 2021 for Humalog and Liprolog as a stand-alone work-sharing submission, (Procedure No. EMEA/H/C/WS2115). A positive opinion of RMP v11.1 was received from PRAC on 02 September 2021. Version 11.1 was also submitted for evaluation with the Lyumjev oKPB line extension, and this evaluation remains ongoing.

Details of the currently approved RMP

Version number: 12.1

Approved with procedure: EMEA/H/C/005037/II/0014

Date of approval (opinion date): 13 October 2022

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Insulin lispro
Pharmacotherapeutic group(s) (ATC Code)	Humalog/Liprolog solution: A10AB04 Humalog/Liprolog Mix25/Humalog/Liprolog Mix50: A10AD04 Lyumjev: A10AB04
Marketing Authorisation Holder	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	2 (Humalog/Liprolog and Lyumjev)
Invented name(s) in the European Economic Area (EEA)	Humalog Liprolog Lyumjev
Marketing authorisation procedure	Centralised Procedure number: Humalog: EMEA/H/C/0088 Liprolog: EMEA/H/C/0393 Lyumjev: EMEA/H/C/5037
Brief description of the product	**Chemical class:** Insulin lispro is produced by recombinant DNA technology utilising a nonpathogenic laboratory strain of *Escherichia coli (E coli)*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analogue and has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin. Humalog/Liprolog is a fast-acting formulation of insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulphate under appropriate conditions for crystal formation. Humalog/Liprolog Mix25 and Humalog/Liprolog Mix50 are premixed suspensions consisting of insulin lispro (rapid-acting human insulin analogue) and insulin lispro protamine suspension formulations. The Lyumjev formulation is a rapid-acting formulation of insulin lispro and includes the enabling excipients citrate and treprostinil, which enable faster insulin absorption and earlier glucose lowering compared to Humalog.
	Summary of mode of action: The primary activity of insulin lispro is the regulation of glucose metabolism. In addition, insulins have several anabolic and anticatabolic actions on a variety of different tissues. Within muscle tissue, this includes increasing glycogen, fatty acid, glycerol and protein synthesis, and amino acid uptake while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism, and amino acid output.

	Humalog/Liprolog 100 and 200 U/mL solution for injection Insulin lispro solution has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within 15 minutes) compared to regular insulin (30 minutes before). Insulin lispro takes effect rapidly and has a shorter duration of activity (2-5 hours) compared to regular insulin.
	Humalog Mix25 and Mix50 100 U/mL suspension for injection and Liprolog Mix25 and Mix50 100 units/mL suspension for injection Humalog/Liprolog Mix25 and Mix50 are premixed suspensions consisting of insulin lispro (rapid-acting human insulin analogue) and insulin lispro protamine suspension (intermediate-acting human insulin analogue). Insulin lispro has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within 15 minutes) compared to insulin mixtures containing regular insulin (30-45 minutes before). The rapid onset and early peak of activity of insulin lispro is preserved following the subcutaneous administration of Humalog/Liprolog Mix25 or Mix50. Insulin lispro protamine suspension has an activity profile that is very similar to that of a basal insulin (NPH) over a period of approximately 15 hours. **Lyumjev 100 and 200U/mL solution for injection** Lyumjev is a formulation of insulin lispro, the same active ingredient used in Humalog. Lyumjev utilises 2 enabling excipients with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection or infusion resulting in a faster insulin time-action profile and in earlier glucose lowering compared to Humalog. These 2 mechanisms include the following: 1. Accelerated absorption of insulin lispro through increased local vasodilation, by adding a microdose of the excipient treprostinil. Treprostinil is a prostacyclin analogue approved for administration by continuous SC or IV infusion for the treatment of pulmonary arterial hypertension (PAH) (Remodulin® product monograph [WWW]; Remodulin SmPC [WWW]; Remodulin USPI 2018). In addition, treprostinil is also marketed for PAH in the United States for administration by inhalation (Tyvaso® packet insert 2018) and oral route (Orenitram® packet insert 2018). 2. Speeding the insulin absorption by enhancing the local vascular permeability, which is achieved by the excipient citrate.
	Important information about its composition: **Humalog/Liprolog 100 U/mL solution for injection** A volume of 1 mL contains 100 U (equivalent to 3.5 mg) of insulin lispro (recombinant DNA origin produced in *E coli*). List of excipients: *m*-Cresol (3.15 mg/mL), glycerol, dibasic sodium phosphate $7H_2O$, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8. **Humalog/Liprolog 200 U/mL solution for injection** A volume of 1 mL contains 200 U (equivalent to 6.9 mg) of insulin lispro (recombinant DNA origin produced in *E coli*). List of excipients: *m*-Cresol (3.15 mg/mL), glycerol, trometamol, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8.

	Humalog/Liprolog Mix25 100 U/mL suspension for injection A volume of 1 mL contains 100 U (equivalent to 3.5 mg) of insulin lispro (recombinant DNA origin produced in *E coli*). Humalog/Liprolog Mix25 consists of 25% insulin lispro solution and 75% insulin lispro protamine suspension. List of excipients: protamine sulphate, *m*-Cresol (1.76 mg/mL), phenol (0.715 mg/mL), glycerol, dibasic sodium phosphate $7H_2O$, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8. **Humalog/Liprolog Mix50 100 U/mL suspension for injection** A volume of 1 mL contains 100 U (equivalent to 3.5 mg) of insulin lispro (recombinant DNA origin produced in *E coli*). Humalog/Liprolog Mix50 consists of 50% insulin lispro solution and 50% insulin lispro protamine suspension. List of excipients: protamine sulphate, *m*-Cresol (2.20 mg/mL), phenol (0.89 mg/mL), glycerol, dibasic sodium phosphate $7H_2O$, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8.
	Lyumjev 100 units/mL A volume of 1 mL contains 100 units (equivalent to 3.5 mg) of insulin lispro (recombinant DNA origin produced in *E. coli*). List of excipients: *m*-Cresol, treprostinil sodium, magnesium chloride hexahydrate, sodium citrate dihydrate, glycerol, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8. **Lyumjev 200 units/mL** A volume of 1 mL contains 200 units (equivalent to 6.9 mg) of insulin lispro (recombinant DNA origin produced in *E. coli*). List of excipients: *m*-Cresol, treprostinil sodium, magnesium chloride hexahydrate, sodium citrate dihydrate, glycerol, zinc oxide, water for injections, hydrochloric acid, and sodium hydroxide may be used to adjust pH to 7.0-7.8. Additional information regarding the enabling excipients Clinically relevant doses of Lyumjev administered subcutaneously contain microdoses of treprostinil, which are not detectable in the systemic circulation or associated with systemic effects. Treprostinil, in the final commercial formulation of Lyumjev, is considered to be an excipient by the CHMP, FDA, and PMDA. The other excipients in the Lyumjev formulation, including sodium citrate, are listed in the FDA Generally Recognized as Safe (GRAS) food additives database and are also within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.
Hyperlink to the Product Information	See 1.13.1
Indication(s) in the EEA	**Current:** **Humalog/Liprolog 100 U/mL solution for injection** For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog/Liprolog is also indicated for the initial stabilisation of diabetes mellitus. **Humalog/Liprolog Mix25 100 U/mL suspension for injection** Humalog/Liprolog Mix25 is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

	Humalog/Liprolog Mix50 100 U/mL suspension for injection Humalog/Liprolog Mix50 is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. **Humalog/Liprolog 200 units/mL KwikPen** For the treatment of adults and paediatric patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog/Liprolog 200 units/mL KwikPen is also indicated for the initial stabilisation of diabetes mellitus. **Lyumjev** Lyumjev is indicated to improve glycaemic control in adults with diabetes mellitus. **Proposed:** **Lyumjev** To improve glycaemic control in paediatric patients with diabetes mellitus.
Dosage in the EEA	**Current:** **Humalog/Liprolog 100 U/mL solution for injection** The dosage should be determined by the physician, according to the requirement of the patient. Humalog/Liprolog may be given shortly before meals. When necessary, Humalog/Liprolog can be given soon after meals. Humalog/Liprolog should be given by subcutaneous injection or by continuous subcutaneous infusion pump and may, although not recommended, also be given by intramuscular injection. If necessary, Humalog/Liprolog may also be administered intravenously (IV); for example, for the control of blood glucose levels during ketoacidosis, acute illnesses, or during intraoperative and postoperative periods. **Humalog/Liprolog Mix25 100 U/mL suspension for injection** The dosage should be determined by the physician, according to the requirement of the patient. Humalog/Liprolog Mix25 may be given shortly before meals. When necessary, Humalog/Liprolog Mix25 can be given soon after meals. Humalog/Liprolog Mix25 should only be given by subcutaneous injection. Under no circumstances should Humalog/Liprolog Mix25 be given intravenously. **Humalog/Liprolog Mix50 100 U/mL suspension for injection** The dosage should be determined by the physician, according to the requirement of the patient. Humalog/Liprolog Mix50 may be given shortly before meals. When necessary, Humalog/Liprolog Mix50 can be given soon after meals. Humalog/Liprolog Mix50 should only be given by subcutaneous injection. Under no circumstances should Humalog/Liprolog Mix50 be given intravenously. **Humalog/Liprolog 200 units/mL KwikPen** The dosage should be determined by the physician, according to the requirement of the patient. Humalog/Liprolog may be given shortly before meals. When necessary, Humalog/Liprolog can be given soon after meals. Humalog/Liprolog 200 units/mL KwikPen solution for injection should only be given by SC. **Lyumjev** Dosing for Lyumjev will be individualised for each patient. Dosing instructions will include the following:

	• Individualise and adjust the dosage of Lyumjev based on the patient's metabolic needs, blood glucose monitoring results, and glycaemic control goal. • Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (that is, amount and type of food, timing of food intake), changes in renal or hepatic function, or during acute illness to minimise the risk of hypoglycaemia or hyperglycaemia. • Administer the bolus dose of Lyumjev at the start of a meal into SC tissue. The bolus dose of Lyumjev can be administered within 20 minutes after starting a meal. • Lyumjev is suitable for continuous subcutaneous insulin infusion (CSII) and multiple daily subcutaneous injections. • Can be administered via IV under close medical supervision.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** **<u>Humalog/Liprolog</u>** • Humalog/Liprolog 100 units/mL solution for injection • Humalog/Liprolog Mix25 100 units/mL suspension for injection • Humalog/Liprolog Mix50 100 units/mL suspension for injection • Humalog/Liprolog 200 units/mL solution for injection **<u>Lyumjev</u>** • Lyumjev 100 U/mL solution for injection • Lyumjev 200 U/mL solution for injection
Is/will the product be subject to additional monitoring in the EU?	No. For Lyumjev, nothing beyond routine additional monitoring as per new MAA that requires the black triangle.

Abbreviations: ATC = Anatomical Therapeutic Chemical; CHMP = Committee for Medicinal Products for Human Use; EU = European Union; FDA = Food and Drug Administration; INN = International Nonproprietary Names; MAA = market authorisation application; NPH = neutral protamine Hagedorn; PMDA = Pharmaceuticals and Medical Devices Agency; RMP = risk management plan.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Type 1 and Type 2 Diabetes Mellitus

Diabetes is a complex, heterogeneous group of diseases characterised by chronic hyperglycaemia (Zimmet et al. 2016). The prevalence of diabetes has been increasing over time and is one of the most common metabolic disorders in the world (Guariguata et al. 2014).

SI.1.1 Incidence

Among existing diabetes incidence data, a few studies suggest that diabetes incidence could be falling despite rising or stable prevalence, but not all data are consistently showing the same trends. Magliano et al (2019) conducted a systematic review of 47 studies reporting trends of diabetes incidence in adults from 1980 to 2017 and showed that in most countries for which data are available, the incidence of diagnosed diabetes was rising from the 1990s to the mid-2000s, after which a pattern emerged of levelling trends in 30% and declining trends in 36% of the reported populations. However, data are limited in low- and middle-income countries where trends in diabetes incidence might be different, including areas where substantial increases in prevalence have been report including the Pacific Islands, Middle East, and South Asia (Magliano et al. 2019).

The Centres for Disease Control and Prevention (CDC) reported that the age-adjusted incidence for adults 18 years and older diagnosed with diabetes in the US was similar in 2000 (6.2 per 1,000 adults) and 2018 (6.9 per 1,000 adults). Compared to adults with diagnosed diabetes aged 18 to 44 years (incidence rate 4.3 per 1000), incidence rates were higher among adults aged 45 to 64 years (9.9 per 1000) and those aged ≥65 years and older (8.8 per 1000) (CDC 2020).

In children and adolescents there are significant regional and national differences in incidence for type 1 diabetes. The incidence of type 1 diabetes among children and adolescents is increasing especially in those ≤15 years old in many countries. The overall annual increase in incidence is estimated to be around 3% with significant geographic differences (IDF 2019). The highest incidence rates per 100,000 population per year for type 1 diabetes in youths (0-14 years) have been observed in Finland (62.3), Sweden (43.2), and Kuwait (41.7) (IDF 2019). Countries with the largest number of children and adolescents with incident type 1 diabetes in 2019 were India (15,900), USA (14,700) and Brazil (7,300) (IDF 2019). In the European region, the largest number in this age group for incident type 1 diabetes in 2019 was UK (3,500) and Germany (2,600) (IDF 2019).

Among US youth ≤20 years old, modelled data for the period 2002-2015 showed that the overall incidence of type 1 diabetes significantly increased (CDC 2020). Data from a large study in the US (SEARCH for Diabetes in Youth Study) showed that between 2014–2015, the estimated annual number of newly diagnosed cases of type 1 diabetes in those <20 years old was 18,291 while in those aged 10-19 years 5,758 were diagnosed with type 2 diabetes (CDC 2020).

SI.1.2 Prevalence

The worldwide prevalence of diabetes (type 1 and type 2 combined, both diagnosed and undiagnosed) continues to increase. The estimated global prevalence in adults aged 20–79 years was 151 million (4.6% of the global population) in 2000 with an increase to 463 million (9.3%) in 2019. It is predicted that 578 million adults (10.2% of the population) will have diabetes by 2030 and 700 million adults (10.9%) will have diabetes by 2045 (IDF 2019). According to the CDC, among the US population overall, it was estimated in 2018 that 34.2 million people of all ages (10.5% of the US population) had diabetes (including undiagnosed diabetes). The prevalence in US adults (≥18 years of age) was higher than the overall population with 34.1 million adults (13.0%) with diabetes (CDC 2020).

Globally, 1.1 million children and adolescents younger than 20 years were estimated to have type 1 diabetes in 2019 (IDF 2019). As with adults, the number of children and adolescents with diabetes is increasing annually. Prevalence of type 1 diabetes was estimated to be approximately 3% globally in children and adolescents in 2019. The prevalence of diabetes differs significantly among regions, with most children and adolescents of European origin diagnosed with type 1 diabetes, while in other populations such as those of Japan origin type 2 diabetes is more prevalent (IDF 2019).

The prevalence of T1D was found to vary substantially, ranging between 0.03 and 1.83 per 1000 up to the year 2000 and between 0.06 and 4.8 per 1000 after 2000 (Dabelea et al. 2014). In the US, the prevalence of T2D in youth (aged 10 to ≤19 years) was 0.34 per 1000 youth in 2001 rising to 0.46 per 1000 in 2009 (Dabelea et al. 2014). Similarly, the estimated prevalence of T2D in adults (age ≥18 years) in 2015 was 9.4% overall, including 25.2% of adults aged ≥65 years (CDC 2017b). Moreover, the prevalence of T2D was shown to be more than double in a population-based UK study from approximately 2.4% in 2000 to 5.3% in 2013 (Sharma et al. 2016).

In 2019, regions with the highest prevalence of children and adolescents (0-14 years) with type 1 diabetes were the European and North American/Caribbean regions with 162,600 and 121,400, respectively. For individual countries, India, USA, and Brazil had the highest prevalence in 2019 with 95,600, 94,200 and 51,500 children and adolescents (0-14 years) with type 1 diabetes, respectively (IDF 2019). In the European region, the highest prevalence in this age group was in Germany (2,600) and UK (3,500) (IDF 2019).

In the US 210,000 children and adolescents (≤20 years of age) or 25 per 10,000 US youths had diagnosed diabetes in 2018. Of those diagnosed with diabetes, 187,000 had type 1 diabetes (CDC 2020). The estimated prevalence in the US of T2D in youth (10-19 years of age) has been increasing over time with 0.34 per 1000 diagnosed in 2001 to 0.46 per 1000 in 2009 (Dabelea et al. 2014)

SI.1.3 Demographics of the Population in the Indication and Risk Factors for the Disease

Overall, the incidence of diabetes appears to be increasing in most populations worldwide, and the rate of increase is greater in low- and middle-income countries than in high-income countries (NCD-RisC 2016).

Age

Diabetes prevalence increases with age; people older than 65 years had the highest prevalence estimated at 135.6 million (19.3%) for the global population in 2019. It is expected there will be a significant increase in aging societies with the number of people over 65 who will have diabetes in 2030 estimated to be 195.2 million (19.6%) and in 2045 to be 276.2 million (19.6%) (IDF 2019). Consistent with global observations, the percentage of adults with diabetes in the US increases with age, with 26.8% ≥65 years old reporting diagnosed and undiagnosed diabetes in 2018, compared to the overall US population (10.5%) and the adult population (13%) (CDC 2020). Globally in 2019 prevalence was lowest among adults aged 20-24 (1.4%) and increased incrementally to 19.9% among adults aged 75-79 (IDF 2019).

Gender

Globally, adult women (aged 20-79 years) have slightly lower prevalence of diabetes compared to men (9.0% vs 9.6%). In 2019, there were about 17.2 million more men than women living with diabetes (prevalence 240.1 million in men and 222.9 million in women). The prevalence of diabetes is expected to increase to 342.5 million (10.8%) in women and 357.7 million (11.1%) in men by 2045 (IDF 2019). Prevalence data from the US adult population in 2018 was consistent with the slightly higher prevalence of 3.9 million (17.9%) in adult men (≥18 years of age) than in adult women who had a prevalence of 3.4 million (16.2%) (CDC 2020).

In paediatric cases, girls and boys are equally affected by T1D, while more girls develop T2D than boys (Diabetes UK 2020 [WWW]; Dabelea et al. 2014; Mayer-Davis et al. 2017). In comparison, slightly more men than women have been diagnosed with T2D in the UK (Diabetes UK 2020 [WWW]) and globally (IDF 2017).

Additional risk factors

Type 1 diabetes mellitus is a multifactorial autoimmune disease determined by the interaction of genetic, environmental, and immunologic factors and has no known prevention mechanism (CDC 2011, 2014).

There are many risk factors associated with T2D. According to World Health Organization Global Report on Diabetes (2016), these risk factors include poor diet, physical inactivity, being overweight or obese, low birth weight, age, ethnicity, gestational diabetes, smoking, and family history.

SI.1.4 Main Existing Treatment Options

Type 1 diabetes mellitus is the clinical manifestation of the body's inability to produce insulin due to autoimmune destruction of the beta cells in the pancreas. Management of T1D typically includes a combination of frequent self-monitoring of blood glucose levels, management of diet and exercise, and insulin therapy as the mainstay of therapy. Insulin treatment for patients with T1D is required for survival and options include basal and prandial insulin given as multiple daily injections, continuous subcutaneous insulin infusion (CSII) by an insulin pump, or inhaled insulin. Treatment for T1D includes analogue insulins which are associated with less hypoglycaemia and weight gain as well as lower haemoglobin A1c (HbA1C) compared with human insulins (ADA 2021).

Patients with T2D should receive the following as first-line therapy:

- lifestyle management,
- diabetes self-management,
- education and support, and
- metformin, if the latter is not contraindicated and is tolerated.

New American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus on management of T2D includes a patient-centred approach with consideration of a history of cardiovascular disease early in the process as well as weight, hypoglycaemic risk, treatment cost, and other patient-related factors (Davies et al. 2018).

For patients with haemoglobin A1c (HbA1c) above target levels, glucose lowering medication selection is patient centred. For patients with clinical cardiovascular disease, a sodium glucose co-transporter-2 (SGLT2) inhibitor or glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease (CKD) or clinical heart failure and cardiovascular disease, an SLGT2 inhibitor with evidence of reducing heart failure and/or CKD progression is recommended.

In patients without established cardiovascular disease or CKD, patient factors including need to minimise hypoglycaemia risk, need to minimise weight gain or promote weight loss, and cost can be considered to guide therapy. If HbA1c remains above target, treatment is intensified with addition of other agents (ADA 2021).

In patients with T2D, insulin therapy may initially include basal insulin with metformin with or without other noninsulin agents. If HbA1c is not controlled, insulin therapy can then be intensified with the addition of prandial insulin or a change to premixed insulin. Advancement to ≥2 prandial insulin injections (or to a basal-bolus insulin regimen) can occur if HbA1c has not reached the target goal (ADA 2021).

Other major classes of pharmacologic therapies, including oral medications and noninsulin injectable agents are available to lower blood glucose levels (Tahrani et al. 2016). All agents listed below are administered orally. Glucagon-like peptide-1 receptor agonists are injectable with semaglutide also available as an oral pill formulation.

- **Metformin,** a biguanide, is usually first-line therapy in patients with T2D. It acts to lower blood glucose, decreasing hepatic glucose production, and other noninsulin mediated mechanisms. Benefits of metformin include extensive experience, no hypoglycaemia, potential for some weight loss, and low cost, while risks include gastrointestinal side effects (ADA 2018). Patients with significant kidney disease cannot use metformin (Tahrani et al. 2016, ADA 2018).
- **Dipeptidyl peptidase-4 (DPP-4) inhibitors** (for example, sitagliptin, linagliptin) are oral drugs that inhibit DPP-4 activity, thereby increasing the levels and duration of action of endogenous GLP-1, which in turn increases insulin secretion. Dipeptidyl peptidase-4 inhibitors are weight neutral and do not have a hypoglycaemia risk with monotherapy (Tahrani et al. 2016) but may have the potential for rare but increased rates of pancreatitis and musculoskeletal side effects (ADA 2018).
- **Sodium glucose co-transporter-2 (SGLT2) inhibitors** (for example, empagliflozin, canagliflozin) promote urinary glucose excretion, which lowers blood glucose by inhibiting an enzyme, which acts to reabsorb glucose from the kidney tubules. These agents promote weight loss and when used alone do not pose a hypoglycaemia risk. There is an increased risk of hypoglycemia when used in combination with insulin and sulphonylureas, therefore, consider reducing the dose of insulin or sulphonylureas when used concomitantly with SGLT2. An increased risk of genitourinary infections, volume depletion, and hypotension may occur with these oral agents (Tahrani et al. 2016). SGLT2 have shown a reduction in heart failure and a progression in CKD (ADA 2021).
- **Glucagon-like peptide-1 (GLP-1) receptor agonists** (for example, dulaglutide, liraglutide and semaglutide) are noninsulin agents that act to lower blood glucose levels by enhancing glucose-dependent insulin secretion by pancreatic beta cells, suppressing elevated glucagon secretion, and delaying gastric emptying, similar to endogenous GLP-1. There is an increased risk of hypoglycemia when used in combination with insulin and sulphonylureas, therefore, consider reducing the dose of insulin or sulphonylureas when used concomitantly with GLP-1. Glucagon-like peptide-1 receptor agonists have an additional benefit of weight loss, but gastrointestinal side effects are common (Tahrani et al. 2016).
- **Sulphonylureas** (for example, glipizide and glimepiride) act through cellular receptors on pancreatic beta cells to promote insulin release. Risks of sulphonylureas include hypoglycaemia and weight gain (Tahrani et al. 2016).
- **Meglitinides** (for example, nateglinide, repaglinide) have a similar mechanism of action and risks as sulphonylureas, with faster onset and shorter duration of actions (Tahrani et al. 2016).
- **Alpha-glucosidase inhibitors (AGIs)** (for example, acarbose, miglitol, and voglibose) inhibit enzymes in intestinal wall cells to delay carbohydrate digestion and absorption. Alpha-glucosidase inhibitors are used more in Asia and can cause gastrointestinal side effects. Risk of hypoglycaemia is low (Tahrani et al. 2016).
- **Thiazolidinediones (TZDs)** (for example, pioglitazone) bind to a nuclear receptor in fat, muscle, liver, and pancreatic beta cells to promote insulin sensitivity, glucose uptake, and

fat formation (Tahrani et al. 2016). Risks of TZDs include oedema, weight gain, and increased risk of bone fractures (Tahrani et al. 2016).

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Worldwide, diabetes is the fifth most common cause of death (Diabetes UK 2012) with the greatest impact seen in countries with large adult populations like Africa, China, India, the US, and Brazil (Guariguata et al. 2014; 2019). Furthermore, diabetes accounted for approximately 10.7% of global all-cause deaths among people 20 to 79 years of age (IDF 2019). Although mortality has decreased, the risk of death among people with diabetes is 2 to 3 times that of people of similar age without diabetes (Zimmet et al. 2016; Zucker et al. 2017).

Type 1 diabetes mellitus mortality risk has decreased over recent decades and varies greatly both geographically and ethnically, with standardised mortality rates ranging from 1.88 in British males to 8.82 in Cuban women (Borchers et al. 2010). Cardiovascular and renal diseases are the leading causes of death for the T1D population in Western nations with longer disease duration; whereas in developing countries with shorter disease duration, acute complications of diabetes and infections constitute the leading causes of death (Borchers et al. 2010; Maahs et al. 2010). Diabetes reduces life expectancy, on average, by more than 20 years in people with T1D (Diabetes UK 2012).

Type 2 diabetes mellitus reduces life expectancy up to 10 years (Diabetes UK 2012) and increases the risk of death by about twice that of people without diabetes (CDC 2011); however, recent studies have demonstrated increasing survival over time (Harding et al. 2014; Read et al. 2016; Holden et al. 2017). The risk of T2D-related death is also related to age. In individuals with T2D under 35 years of age, 75% of all deaths were attributable to diabetes, decreasing to 59% among those aged 35 to 64 years and 29% among those aged 64 years or older (Roglic et al. 2005).

Type 1 diabetes mellitus burden can be difficult to calculate; however, achieving normoglycaemia is an important therapeutic goal for patients with T1D as this is necessary to avoid or minimise complications. For example, the risk for microvascular complications including retinopathy, nephropathy, and neuropathy decreases with intensive insulin therapy (Atkinson et al. 2014). Regarding macrovascular complications, cardiovascular disease is becoming more common among patients with T1D as their survival increases; accordingly, patients with T1D have a 10 times higher risk for cardiovascular events such as myocardial infarction, stroke, angina, and the need for coronary-artery revascularisation (Orchard et al. 2006; Atkinson et al. 2014).

Similarly, T2D is associated with significant morbidity including macrovascular and microvascular complications (Shah et al. 2015). Cardiovascular disease is the leading complication and can include: peripheral arterial disease, heart failure, stable angina, nonfatal myocardial infarction, and stroke among others; approximately half of patients with T2D will die of a cardiovascular cause (van Dieren et al. 2010; Shah et al. 2015). Microvascular complications include nephropathy, retinopathy, and neuropathy and then further sequelae of these

complications exacerbated by other comorbidities, such as lower extremity amputations. Approximately 10% of patients with diabetes die of renal failure (van Dieren et al. 2010).

SI.1.6 Important Co-morbidities

The important comorbidities that may occur among patients with diabetes mellitus are listed below:

Comorbidity	Expected Magnitude of Comorbidity (Prevalence)	Expected Co-medications of Comorbidity
Obesity	Canada: DM: 74% (Slater et al. 2011) Germany (youth) T1D: 12.6% (Go et al. 2014) Germany (youth) T2D: 79.4% (Go et al. 2014); Germany: 31.13% Southern Germany (Boehme et al. 2015) UK: 29.5% (Girman et al. 2012);	Weight loss drugs, lipase inhibitors, appetite suppressants
Cardiovascular Disease		
Myocardial Infarction	Sweden: 2.4% T1D and 9.1% T2D (Rawshani et al. 2017)	Vasodilators, cardiac depressant drugs, antiarrhythmic drugs, antithrombotic drugs, thrombolytic drugs
Stroke	Germany: 4.15% T2D (Boehme et al. 2015) Sweden: 1.6% T1D and 6.6% T2D (Rawshani et al. 2017)	Antihypertensives, anticoagulants, antiplatelets
Coronary Heart Disease	Germany: 22.99% (Boehme et al. 2015) Sweden: 4.7% T1D and 17.3% T2D (Rawshani et al. 2017)	Cholesterol-modifying medications, beta blockers, aspirin, calcium channel blockers, ranolazine, nitroglycerine, ACE inhibitors, and angiotensin II receptor blockers
Heart Failure	Denmark: 3.6% DM chronic heart failure (Pallisgaard et al. 2016) Sweden: 1.5% T1D and 6.7% T2D (Rawshani et al. 2017)	Diuretics, vasodilators, cardiostimulatory/inotropic drugs, cardioinhibitory drugs, SGLT2 inhibitors
Hypertension	Finland: 15.2% T1D <30 years of age (Reunanen et al. 2000) Italy: 66.6% T2D (Colivicchi et al. 2007) Germany: 77.0% T2D age- and sex-standardised (Boehme et al. 2015) Denmark: 20.0% DM (Pallisgaard et al. 2016)	Beta blockers, calcium channel blockers, ACE inhibitors and angiotensin II receptor blockers, direct renin inhibitors, diuretics
Hyperlipidaemia	US: LDL >100 mg/dL without treatment, T2D: 28% (Brandle et al. 2003); 93.5% (Mody et al. 2007); 77.2% (Iglay et al. 2016); 61.5% ever high cholesterol (Lopez et al. 2014).	Lipid-modifying medications

Comorbidity	Expected Magnitude of Comorbidity (Prevalence)	Expected Co-medications of Comorbidity
	T2D patients receiving cholesterol medication: 30% (Brandle et al. 2003) LDL-C level >130 mg/dL, T1D patients: 15%; T2D patients: 24% (Kershnar et al. 2006)	
Nephropathy/ Microalbuminuria	Nephropathy EU, T1D: 30.5% (Toeller et al. 1999) Microalbuminuria EU, T1D: 8.8% (Toeller et al. 1999) Sweden: 7.7% T1D and 8.5% T2D (Rawshani et al. 2017) End-stage kidney disease Sweden: 1.2% T1D and 0.2% T2D (Rawshani et al. 2017) Germany: 7.57% T2D renal insufficiency (Boehme et al. 2015) Denmark: 1.6% DM chronic kidney disease (Pallisgaard et al. 2016) 2.0% T2D ever experienced moderate-to-severe kidney disease and 4.4% kidney disease (Lopez et al. 2014)	ACE inhibitors and angiotensin II receptor blockers
Retinopathy	EU: 46.7% T1D (Toeller et al. 1999) Scotland: 32.5% (Ding et al. 2010) Germany: 24.83% T2D southern Germany (Boehme et al. 2015)	VEGF inhibitors, corticosteroids, ophthalmics
Neuropathy	UK: up to 50% of the DM population (Diabetes UK 2012); 26.4% T2D (Davies et al. 2006)	Antiseizure drugs, antidepressants
Sexual Dysfunction	Erectile Dysfunction Global Literature Review: 35% T1D and 90% T2D (Malavige and Levy 2009)	PDE-5 inhibitors
Neoplasms	Italy: overall cancer incidence among diabetes patients is 15% to 30% higher than among those without diabetes (Ballotari et al. 2017) Denmark: lifetime risk of both diabetes and cancer is approximately 15% (Carstensen et al. 2014)	Chemotherapy, immunotherapy

Abbreviations: ACE = angiotensin-converting enzyme; DM = diabetes mellitus; EU = European Union; LDL = low density lipoprotein; LDL-C = LDL cholesterol; PDE-5 = phosphodiesterase type 5; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; UK = United Kingdom; US = United States; VEGF = vascular endothelial growth factor.

Module SII - Nonclinical Part of the Safety Specification

SII.1 Toxicity

The effect of insulin lispro given parenterally to laboratory animals in single-dose and repeated-dose toxicology studies has been the expected finding of lowered blood glucose. In chronic toxicity studies, lowering of blood glucose was accompanied by changes in serum lipids and body weight gain. Insulin lispro demonstrated no mutagenic, immunogenic, teratogenic, or reproductive effects, and did not produce in vivo proliferative effects or tumours in organs and tissues when given at very high SC doses in chronic toxicity tests. Thus, the findings in toxicology studies support the safety of insulin lispro for parenteral use in humans for the treatment of diabetes.

Insulin lispro was compared with human insulin and was found to be equipotent in terms of binding to the human placental insulin receptor and in stimulating [14C] glucose uptake into rat adipocytes. In a subsequent study, insulin lispro and human insulin were shown to have nearly identical dissociation kinetics from the human HepG2 insulin receptor, whereas Asp(B10) human insulin dissociated from the human insulin receptor at a rate approximately 50% that of either insulin lispro or human insulin. Insulin lispro has been shown to be slightly more potent (approximately 1.6 times) than human insulin in binding to the human placental insulin-like growth factor-1 (IGF-1) receptor.

In 1 study, insulin lispro was found to be approximately 2 times more potent than human insulin at stimulating [3H] thymidine incorporation into human aortic smooth muscle cells (a measure of cellular proliferation); while in another study, insulin lispro and human insulin were equipotent at stimulating growth of human mammary epithelial cells (median effective dose [ED50] insulin, 16.0±3.0 nM; ED50 insulin lispro, 18.6±4.0 nM, n=4, p=not significant). In both studies, an Asp(B10) insulin analogue was 3 to 15 times more potent than either human insulin or insulin lispro. These in vitro studies demonstrated a low potential for proliferative activity with insulin lispro.

SII.2 Safety Pharmacology

No significant cardiovascular effects or serious adverse effects of insulin lispro on renal function were observed. Effects of insulin lispro on smooth and cardiac muscle at the highest concentration tested were not considered clinically relevant.

SII.3 Other Toxicity-Related Information or Data

The following is specific to Lyumjev:

In vitro hERG and in vivo cardiovascular safety pharmacology (dog) studies of the excipient treprostinil confirmed previously reported findings of QT/QTc prolongation in dogs and humans that were not due to blockade of hERG (Guideri et al. 2006; FDA 2013; Tyvaso USPI [WWW]). The no-observed-adverse-effect level for these effects in the cardiovascular safety pharmacology study was 0.004 mg/kg (49.4× the maximum observed drug concentration [C_{max}] of a high anticipated treprostinil dose of 1500 ng in human subjects [equivalent to a 150-unit dose of

100-unit/mL Lyumjev]). The cardiovascular effects at the higher doses (≥15 000 ng/kg) in dogs should not be a concern for patients with diabetes because of the microdoses of treprostinil used in Lyumjev (≤5 ng/kg, 3 times daily).

Repeat SC dosing with treprostinil for up to 26 weeks was well-tolerated in rats and dogs at doses up to 0.1 mg/kg/day and 0.07 mg/kg/day, respectively. No evidence of injection site reactions occurred either when treprostinil was injected alone in 13- or 26-week repeat-dose toxicity studies in rats and dogs or when treprostinil was injected alone or in combination with insulin lispro (that is, Lyumjev) in a 2-week, local tolerance study in rats. There was no indication of direct target organ toxicity in either rats or dogs.

No evidence of genotoxicity was demonstrated with treprostinil in a standard battery of genetic toxicity tests.

Treprostinil did not produce evidence of reproductive toxicity or teratogenicity in rats and no evidence of teratogenicity in rabbits.

Module SIII - Clinical Trial Exposure

Humalog

Table SIII.1. Duration of Humalog (LY275585) Exposure

Cumulative for all indications (person time)		
Duration of exposure	**Patients (N=21,403)**	**Person time (years)**
1 day	280	0.77
1 day < exposure ≤ 1 month	1161	33.71
1 month < exposure ≤ 3 months	4226	870.96
3 months < exposure ≤ 6 months	8937	3743.81
6 months < exposure ≤ 12 months	3026	2347.33
12 months < exposure ≤ 18 months	447	650.49
18 months < exposure ≤ 24 months	1434	2586.64
24 months < exposure ≤ 30 months	63	157.50
30 months < exposure ≤ 36 months	168	480.75
36 months < exposure ≤ 42 months	1081	3783.50
42 months < exposure ≤ 48 months	580	2320.00
Total person time	21,403	16,975.46

Abbreviation: N = total number of subjects who have taken Humalog.
Note 1: Treatment duration is used to estimate duration of exposure.
Note 2: LY275585 includes all subjects allocated to receive LY275585, combined across all doses of LY275585.
Note 3: Treatment duration was not available for Study I8B-FW-ITRA.
Source: /lillyce/prd/ly275585/rmpapr2017/output/siii2_2019.rtf.

Table SIII.2. Humalog Exposure by Age Group and Gender

Age group	Patients				Person time (years)			
	Male (N=9273)	**Female (N=8557)**	**Unknown Gender (N=3573)**	**Total (N=21,403)**	**Male**	**Female**	**Unknown Gender**	**Total**
<12 years	40	65	6	111	25.42	35.00	2.76	63.18
≥12 and <18 years	546	504	40	1090	183.00	158.50	16.10	357.60
≥18 and <65 years	4892	4642	642	10,176	3903.32	3549.77	315.44	7768.54
≥65 years	1224	1048	136	2408	702.56	640.25	101.78	1444.59
Adult ≥18 years, unspecified	2111	1972	1227	5310	1868.61	1661.84	408.00	3938.45
Unknown Age	460	326	1522	2308	681.34	487.35	2234.41	3403.10
Total	9273	8557	3573	21,403	7364.24	6532.71	3078.50	16,975.46

Abbreviation: N = total number of subjects who have taken Humalog.
Note 1: Treatment duration is used to estimate duration of exposure.
Note 2: LY275585 includes all subjects allocated to receive LY275585, combined across all doses of LY275585.
Note 3: Treatment duration was not available for Study I8B-FW-ITRA.
Note 4: Unknown Age (Gender) is defined as Age (Gender) was not reported.
Source: /lillyce/prd/ly275585/rmpapr2017/output/siii7_2019.rtf.

Table SIII.3. Humalog Exposure by Ethnic Origin

Ethnic origin	Patients (N=21,403)	Person time (years)
Asian	3184	1724.57
Black	491	291.19
Caucasian	11,539	9232.02
Multiple	17	7.21
Other	1329	842.24
Unknown	4843	4878.22
Total	21,403	16,975.46

Abbreviation: N = total number of subjects who have taken Humalog.
Note 1: Treatment duration is used to estimate duration of exposure.
Note 2: LY275585 includes all subjects allocated to receive LY275585, combined across all doses of LY275585.
Note 3: Treatment duration was not available for Study I8B-FW-ITRA.
Note 4: Unknown: Ethnicity information was not reported.
Source: /lillyce/prd/ly275585/rmpapr2017/output/siii9_2019.rtf.

Lyumjev

The clinical trial exposure for Lyumjev (LY900014) includes data to 16 July 2021.

Table SIII.4. Duration of Lyumjev Exposure in Paediatric Phase 3 Studies

Cumulative for All Indications **(person time)**		
Duration of Exposure	**Patients (N)**	**Person Time (patient-years)**
<1 month	5	0.19
1 to <3 months	8	1.36
3 to <6 months	44	20.39
≥6 months	361	183.13
Total	**418**	**205.07**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.
Note: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, or at 20 minutes after start of a meal.
Source: \prd\ly900014\i8b_mc_itsb\final\output\shared\smexp05.

Table SIII.5. Duration of Lyumjev Exposure in Adult Phase 3 Studies

Cumulative for All Indications **(person time)**		
Duration of Exposure	**Patients (N)**	**Person Time (patient-years)**
<1 month	64	3.76
1 to <3 months	104	13.83
3 to <6 months	321	118.75
≥6 months	1453	978.00
Total	**1942**	**1114.34**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.

Note: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, immediately after completion of a meal, or at 20 minutes after start of a meal.
Source: prd\ly900014\regulatory_oct2021\output\shared\ t_rmp_ph3_exp1.

Table SIII.6. Lyumjev Exposure by Age Group and Gender in Paediatric Phase 3 Studies

Cumulative for All Indications						
Age Group	**Patients (N)**			**Person Time (patient-years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Children						
1 to <6 years	10	10	20	5.03	5.07	10.11
6 to <12 years	67	61	128	33.46	29.83	63.29
12 to <18 years	132	138	270	65.51	66.16	131.67
Total	**209**	**209**	**418**	**104.00**	**101.07**	**205.07**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.
Note: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, or at 20 minutes after start of a meal.
Source: \prd\ly900014\i8b_mc_itsb\final\output\shared\smexp06.

Table SIII.7. Lyumjev Exposure by Age Group and Gender in Adult Phase 3 Studies

Cumulative for All Indications						
Age Group	**Patients (N)**			**Person Time (patient-years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Children (2-11 years)	0	0	0	0	0	0
Adolescent (12-17 years)	1	0	1	0.28	0	0.28
Adults (18 to 64 years)	830	754	1584	506.69	424.32	931.01
Elderly	207	150	357	109.32	73.73	183.05
65 to 74 years	186	140	326	97.58	68.69	166.27
75 to 84 years	20	10	30	11.58	5.04	16.62
≥85 years	1	0	1	0.16	0	0.16
Total	**1038**	**904**	**1942**	**616.30**	**498.05**	**1114.34**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.
Note: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, immediately after completion of a meal, or at 20 minutes after start of a meal.
Source: prd\ly900014\regulatory_oct2021\output\shared\t_rmp_ph3_exp3.

Table SIII.8. Lyumjev Exposure by Age Group and Gender in Clinical Pharmacology Studies

Age Group	*Development Formulation*				*Final Formulation*			
	Subjects (N)		Number of Doses		Subjects (N)		Number of Doses	
	Male	Female	Male	Female	Male	Female	Male	Female
Total								
Children (2-11 years)	0	0	0	0	5	11	8	29
Adolescent (12-17 years)	0	0	0	0	11	5	30	11
Adults (18 to 64 years)	**116**	**26**	**1917**	**511**	415	107	2466	701
Elderly	**8**	**1**	**149**	**3**	51	21	161	22
65 to 74 years	**8**	**1**	**149**	**3**	50	21	160	22
75 to 84 years	**0**	**0**	**0**	**0**	**1**	**0**	**1**	**0**
≥85 years	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.

Note: Lyumjev administration varied between 15 minutes before start of a meal, immediately before start of a meal, 15 minutes after start of a meal, or 20 minutes after start of a meal.

Source: prd\ly900014\regulatory_oct2021\output\shared\t_rmp_cp_exp03.

Table SIII.9. Lyumjev Exposure by Ethnic Origin in Paediatric Phase 3 Studies

Cumulative for All Indications **(person time)**		
Ethnic Origin	**Patients (N)**	**Person Time (patient-years)**
Hispanic or Latino	91	44.40
Not Hispanic or Latino	270	132.43
Unknown	57	28.24
Total	**418**	**205.07**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.

Note 1: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, or at 20 minutes after start of a meal.

Note 2: Unknown ethnicity refers to nonreported ethnicity.

Source: \prd\ly900014\i8b_mc_itsb\final\output\shared\smexp03.

Table SIII.10. Lyumjev Exposure by Ethnic Origin in Adult Phase 3 Studies

Cumulative for All Indications **(person time)**		
Ethnic Origin	**Patients (N)**	**Person Time (patient-years)**
Hispanic or Latino	186	106.13
Not Hispanic or Latino	1255	760.63
Unknown	501	247.59
Total	**1942**	**1114.34**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.

Note 1: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, immediately after completion of a meal, or at 20 minutes after start of a meal.

Note 2: Unknown ethnicity refers to nonreported ethnicity.

Source: prd\ly900014\regulatory_oct2021\output\shared\t_rmp_ph3_exp4.

Table SIII.11. Lyumjev Exposure by Ethnic Origin in Clinical Pharmacology Studies

Cumulative for All Indications **(person time)**	**Development Formulation**		**Final Formulation**	
Ethnic Origin	**Subjects (N)**	**Number of Doses**	**Subjects (N)**	**Number of Doses**
Total				
Hispanic or Latino	0	0	4	7
Not Hispanic or Latino	151	2580	591	3132
Unknown	0	0	31	289

Abbreviations: N = number of subjects.

Note 1: Lyumjev administration varied between 15 minutes before start of a meal, immediately before start of a meal, 15 minutes after start of a meal, or 20 minutes after start of a meal.

Note 2: Unknown ethnicity refers to nonreported ethnicity.

Note 3: T1D Pump - Patients also received continuous infusion of Lyumjev during treatment periods.

Source: prd\ly900014\regulatory_oct2021\output\shared\t_rmp_cp_exp04.

Table SIII.12. Lyumjev Exposure by Racial Origin in Paediatric Phase 3 Studies

Cumulative for All Indications **(person time)**		
Racial Origin	**Patients (N)**	**Person Time (patient-years)**
American Indian or Alaska Native	6	2.96
Asian	20	9.67
Black or African American	4	1.79
White	382	187.91
Multiple	1	0.66
Unknown	5	2.09
Total	**418**	**205.07**

Abbreviation: N = number of patients exposed to at least 1 Lyumjev dose.

Note 1: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, or at 20 minutes after start of a meal.

Source: \prd\ly900014\i8b_mc_itsb\final\output\shared\smexp04.

Table SIII.13. Lyumjev Exposure by Racial Origin in Adult Phase 3 Studies

Cumulative for All Indications (person time)		
Racial Origin	**Patients (N)**	**Person Time (patient-years)**
American Indian or Alaska Native	18	9.11
Asian	644	380.52
Black or African American	35	18.34
Native Hawaiian or other Pacific Islander	0	0
White	1209	682.98
Multiple	33	21.74
Unknown	3	1.65
Total	**1942**	**1114.34**

Abbreviations: N = number of patients exposed to at least 1 Lyumjev dose.

Note 1: Lyumjev exposure includes Lyumjev administration at 0 to 2 minutes prior to start of a meal, or at 20 minutes after start of a meal.

Source: prd\ly900014\regulatory_oct2021\output\shared\t_rmp_ph3_exp2.

Table SIII.14. Lyumjev Exposure by Racial Origin in Clinical Pharmacology Studies

Cumulative for All Indications (person time)	Development Formulation		Final Formulation	
Racial Origin	**Subjects (N)**	**Number of Doses**	**Subjects (N)**	**Number of Doses**
Total				
American Indian or Alaska Native	0	0	2	5
Asian	61	211	222	650
Black or African American	0	0	1	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	90	2369	396	2760
Multiple	0	0	5	12
Unknown	0	0	0	0

Abbreviation: N = number of subjects.

Note 1: Lyumjev administration varied between 15 minutes before start of a meal, immediately before start of a meal, 15 minutes after start of a meal, or 20 minutes after start of a meal.

Note 2: Unknown race refers to nonreported race.

Note 3: T1D Pump - Patients also received continuous infusion of Lyumjev during treatment periods.

Source: \prd\ly900014\regulatory_oct2021\output\shared\ t_rmp_cp_exp02.

Module SIV - Populations Not Studied in Clinical Trials

Humalog has been used in clinical practice for over 20 years. Millions of patients in all age and gender groups, ethnic and racial backgrounds, and with and without pre-existing conditions have been exposed to Humalog for long periods of time.

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The previous exclusion criteria in the earlier development of Humalog are not relevant after millions of patients have been exposed over multiple years.

Extensive experience with Humalog can be applied to Lyumjev in the following populations:

Criterion: Women who are pregnant

Reason for exclusion: This is a standard exclusion criterion in clinical development including in Lyumjev studies.

Is it considered to be included as missing information? No

Rationale: Pregnant women were not included in Lyumjev studies. However, Humalog, which contains the same active ingredient as Lyumjev, has been used in clinical practice for over 20 years. As treatment with insulin is required in patients with T1D, this sizeable exposure includes patients who are pregnant. Though not included in prospective clinical trials, use of Humalog in pregnant women is well established in the published literature (de Jong et al. 2016) and clinical treatment guidelines (ADA 2018 [Management of Diabetes in Pregnancy]). Published observational studies also support the efficacy and safety of Humalog in pregnant women (de Jong et al. 2016).

Criterion: Renal and hepatic impairment

Reason for exclusion: The associated comorbidities/concomitant medications in patients with significant renal or hepatic impairment might represent an important confounder in clinical trials. The Lyumjev Phase 3 development programme included the following standard renal and hepatic exclusion criteria:

> Renal: History of renal transplantation, currently receiving renal dialysis, serum creatinine >2.0 mg/dL (177 µmol/L) at screening.
>
> Hepatic: Have obvious clinical signs or symptoms of liver disease (for example, acute or chronic hepatitis or cirrhosis), or elevated liver enzyme measurements as indicated below at screening:
>
> a) Total bilirubin level (TBL) ≥2 times the upper limit of normal (ULN [with the exception of Gilberts Disease]) as defined by the central laboratory,
>
> *Or*

b) Alanine aminotransferase (ALT) ≥3 times ULN as defined by the central laboratory,

Or

c) Aspartate aminotransferase (AST) ≥3 times ULN as defined by the central laboratory

Is it considered to be included as missing information? No

Rationale: Insulin dosing is individualised for each patient based on clinical factors including glycaemic control, hypoglycaemia risk, as well as comorbidities. Insulin requirements may be reduced in the presence of renal or hepatic impairment (Humalog summary of product characteristics [SmPC] [WWW]; Humalog USPI [WWW]). Patients with renal or hepatic impairment may be at increased risk of hypoglycaemia and may require more frequent insulin dose adjustment and more frequent glucose monitoring. Lyumjev treatment in patients with renal or hepatic impairment would be expected to be similar to Humalog.

Treprostinil is mainly cleared via metabolism mediated by cytochrome (CYP)2C8, and to a lesser extent by CYP2C9 (Peterson et al. 2013). However, use of Lyumjev in hepatically impaired subjects, and coadministration of a strong CYP2C8 inhibitor or a strong CYP inducer is not expected to result in a clinically meaningful change in systemic treprostinil exposure (Remodulin USPI [WWW]). If Lyumjev was coadministered with strong CYP2C8 inhibitors or CYP inducers, local treprostinil concentrations will remain within the therapeutic window. As an enabling excipient, treprostinil is not expected to be a perpetrator of clinically relevant drug interactions with other drugs. Treprostinil in Lyumjev is administered as a microdose that does not have a systemic effect but only a local vasodilatory effect, and hence systemic treprostinil concentrations are too low to inhibit or induce the metabolism or transport of other drugs.

Lilly has conducted clinical studies evaluating the safety and efficacy of Humalog in patients with renal (Study F3Z-MC-IOEI [IOEI]) and hepatic (Study F3Z-MC-IOEK [IOEK]) impairment. Although the pharmacokinetic profile of insulin lispro was independent of renal function, T2D patients with end-stage renal disease were more sensitive to the glucose lowering effects of insulin lispro compared to patients with normal renal function (Study IOEI). Hepatic impairment did not affect the SC insulin absorption, general disposition, or postprandial blood glucose excursion profiles of insulin lispro in T2D patients (Study IOEK). Similar results were documented with regular human insulin in both studies. Additionally, postmarketing safety surveillance has revealed no signals or additional risks when Humalog is used in these populations. Nevertheless, as insulin requirements may vary dependent on renal and hepatic function, individual titration is required as for all insulins.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Extensive experience with Humalog, which has been used in clinical practice for the past 25 years, can be applied to Lyumjev because Lyumjev contains the same active ingredient as Humalog. Millions of patients in all age and gender groups, with and without pre-existing

conditions, have been exposed to Humalog for long periods of time, providing insights into rare adverse reactions and those with a long latency.

Table SIV.1. Ability to Detect Adverse Reactions (Limitation of Trial Programme)

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	N/A	Rapid acting insulin analogues have been administered to millions of patients for many years. The MAH has no knowledge of rare conditions beyond those listed in the label developing in patients using insulin lispro.
Due to prolonged exposure	N/A	Rapid acting insulin analogues have been administered to millions of patients for many years and are typically used for chronic treatment of patients with diabetes. The MAH has no knowledge of adverse reactions developing due to prolonged exposure to insulin lispro, other than those in current label.
Due to cumulative effects	N/A	Rapid acting insulin analogues have been administered to millions of patients for many years. There are no known cumulative effects from insulin lispro.
Which have a long latency	N/A	Rapid acting insulin analogues have been administered to millions of patients for many years. The MAH has no knowledge of particular adverse reactions with long latency developing with insulin lispro.

Abbreviations: MAH = marketing authorisation holder; N/A = not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.2. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric	Use of Humalog in paediatric patients has increased steadily over the years since it was approved over 25 years ago. It is now widely used and considered with other rapid-acting insulin analogues to be an important treatment option for paediatric patients (Kapellen et al. 2009; Kaiserman et al. 2017). Humalog is licensed for the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis (SmPC). This indication statement includes adults and children. It has been widely used in children. It is considered safe and effective when used either through daily injections timed with meals or continuous subcutaneous insulin infusion therapy (Galli-Tsinopoulou and Stergidou 2012). The clinical efficacy and safety of Humalog in very young children (for example, infants and neonates) have not been studied as extensively as in the adult population.
	The safety profile of Lyumjev has been established in 2 clinical studies in paediatric patients. A randomised, 2-period crossover study (ITSA) in children (6 to <12 years of age) and adolescents (12 to <18 years of age) with T1D was conducted to evaluate PK, GD, safety, and tolerability of Lyumjev compared to Humalog. A total of 27 (6 to <12 n=13; 12-<18 n= 14) paediatric patients received Lyumjev, which was well tolerated following a single SC bolus given as an injection or infusion in both age groups. Study ITSB was a safety and efficacy study conducted in 716 paediatric patients ages 1-17 with T1D. In this study, a total of 418 paediatric patients received Lyumjev. Of these, 361 received Lyumjev for at least 180 days. In Studies ITSA and ITSB, the safety of Lyumjev was similar to Humalog.

Type of Special Population	Exposure
Elderly	The American Geriatrics Society guidelines suggest an HbA1c target of 8.0% in frail geriatric patients with diabetes (Moreno et al. 2013). Achievement of glycaemic control in geriatric patients is complicated by many factors, such as age-related decline in physical and cognitive functions, difficulty in achieving dietary and exercise goals, presence of multiple co-morbidities, polypharmacy, and increased risk for AEs, particularly hypoglycaemia (Mooradian 2011; Moreno et al. 2013). A review paper in 2011 (Mannucci et al. 2011) concluded that insulin therapy in elderly subjects with T2D has not been adequately investigated. The few available studies included a small number of patients, and none of them compares elderly with younger adult patients. Given that older people on insulin treatment are often excluded from clinical trials, the number of published subgroup analyses limited to elderly is also small. Available trials are insufficient to establish the superiority of one or another regimen of insulin therapy in elderly patients.
	Refer to Table SIII.7 and Table SIII.8 for elderly exposure in the Lyumjev clinical development programme.
Pregnant or breastfeeding women	Pregnant women were not included in the clinical development programme for Humalog. Data on a large number of exposed pregnancies do not indicate any adverse effect of Humalog in pregnancy (Humalog SmPC).
	Pregnancy was an exclusion criterion in the Lyumjev clinical development programme. Breastfeeding women were not included in the Lyumjev clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Insulin requirements may change significantly in patients with hepatic impairment (SmPC). One clinical trial (Study F3Z-MC-IOEK) determined the influence of hepatic impairment on the pharmacokinetics and glucodynamics of Humalog and regular human insulin in patients with T2D either without hepatic dysfunction (n=6) or with IR associated with chronic hepatitis or cirrhosis (n=14). Hepatic impairment did not affect the subcutaneous insulin absorption, general disposition, or postprandial blood glucose excursion profiles of Humalog or regular human insulin.
	Patients with obvious liver disease or with ALT or AST ≥3 times ULN or total bilirubin ≥2 times ULN were not included in the Lyumjev Phase 3 clinical development programme. Not studied in patients with severe hepatic impairment.

Type of Special Population	Exposure
Patients with renal impairment	Insulin requirements may change significantly in the presence of renal impairment (SmPC). Study F3Z-MC-IOEI was an open-label, randomised, crossover study comparing the pharmacokinetics and glucodynamics of Humalog and regular human insulin in 25 patients with T2D and varying degrees of renal function. Although the pharmacokinetics of the 2 insulins were independent of renal function, patients with end-stage renal disease were more sensitive to the glucose-lowering effects of both insulins compared to patients with normal renal function.
	A total of 88 patients with moderate renal impairment at baseline eGFR (<60 mL/min/1.73 m^2) were included in the Lyumjev treatment groups[a] in the Phase 3 clinical development programme (31 in T1D MDI, 57 in T2D MDI, and none in T1D pump study).
Patients with cardiovascular impairment	Cardiovascular disease is the leading cause of morbidity and mortality for patients with diabetes (ADA 2018). Patients with Class III or IV heart failure, based on the NYHA classification, were excluded from studies in the Humalog clinical development programme; however, pooled data from earlier trials in the clinical development programme show no effect of Humalog on development of cardiovascular disease or worsening of preexisting cardiovascular disease or symptoms (Glazer 1999). Observational studies comparing Humalog to other rapid-acting insulins found no differences in cardiovascular disease and event safety endpoints (Lak et al. 2016; Svensson et al. 2017). Patients with diabetes taking TZDs and Humalog should be monitored for signs and symptoms of heart failure, and reduction in dose or discontinuation of Humalog should be considered if heart failure occurs (USPI 2018).
	Cardiovascular disease is a common comorbidity in patients with diabetes (Baena-Díez et al. 2016). Patients with cardiovascular disease, within the last 6 months prior to screening, defined as stroke, decompensated heart failure NYHA class III or IV, myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft were not included in the Lyumjev Phase 3 clinical development programme.
Immunocompromised patients	Immunocompromised patients were not included in the Humalog clinical development programme.
	Not included in the Lyumjev clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Humalog and Lyumjev clinical trials specified the degree of diabetes severity by inclusion criteria such as baseline glycosylated haemoglobin (HbA1c), diabetes duration, and use of other diabetes medications (in T2D only). The number of patients and exposure time are the same as that for the overall clinical programme.
Population with relevant different ethnic origin	Patients with diabetes from different racial and ethnic backgrounds were included in the Humalog clinical development program. The number of patients and exposure time are shown in Table SIII.3.

Type of Special Population	Exposure
	Patients with diabetes from different racial and ethnic backgrounds were included in the Lyumjev clinical development programme. The numbers of patients and exposure time are the shown in Table SIII.9 and Table SIII.12.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations of patients with diabetes carrying relevant genetic polymorphisms were not specifically assessed in the Humalog and Lyumjev clinical development programmes.
Other	Not applicable.

Abbreviations: ADA = American Diabetes Association; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HbA1c = haemoglobin A1c; MDI = multiple daily injections; MAA = marketing authorisation application; NYHA = New York Heart Association; PD = pharmacodynamic; PK = pharmacokinetic; SmPC = summary of product characteristics; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; TZD = thiazolidinediones; ULN = upper limit of normal.

[a] Lyumjev treatment groups included Lyumjev administration at 0 to 2 minutes prior to start of a meal, immediately after completion of a meal, or at 20 minutes after start of a meal.

Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide sales of Humalog and Lyumjev have been collected for the cumulative time period ending on 30 September 2021. These data are the basis for calculating global patient exposure estimates for Humalog and Lyumjev. Patient exposure estimates are calculated from the total units of Humalog and Lyumjev sold, divided by the number of units used by an assumed "typical" diabetic patient in 1 year, estimated for Humalog to be 25 U/day or 9125 U/year. Calculations are expressed in terms of patient-years (PY) of treatment, assuming that once a patient begins insulin it is continued.

SV.1.2 Exposure

Humalog (LY275585)

Cumulative PY of treatment are estimated to be 123.36 million (3.32 million from Lispro U-200 and 120.05 million from all other formulations). Table SV.1 provides a summary of patient exposure estimates in patient-years by region cumulatively to 30 September 2021.

Table SV.1. Geographical Summary of Sales and Exposure for Humalog (LY275585) Cumulatively through 30 September 2021

Country/Countries	Sales (in millions of units)		Estimated patient exposure in patient years	
	Lispro (all other Formulations)	U-200	Lispro (all other Formulations)	U-200
European Union[a]	320,396	21,858	35,111,000	2,395,000
Japan	[redacted]	N/A	[redacted]	-
United States	[redacted]	[redacted]	[redacted]	[redacted]
Other Countries	330,831	[redacted]	36,255,000	[redacted]
Global Totals	1,095,452	30,295	120,049,000[b]	3,319,000[b]

Abbreviation: N/A = not applicable.

[a] The EU countries represented here are Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

[b] Global total may not sum due to independent rounding.

Note: U-200 formulation is not marketed in Japan.

Lyumjev (LY900014)

Cumulative PY of treatment are estimated to be 89,000 (23,000 from Lispro U-200 and 66,000 from all other formulations).

Table SV.2. Geographical Summary of Sales and Exposure for Lyumjev® (LY900014) Cumulatively through 30 September 2021

Country/Countries	Sales (in units)		Estimated patient exposure in patient years	
	Lispro (all other formulations)	U-200	Lispro (all other formulations)	U-200
European Union[a]	321,947,500	197,056,500	35,000	21,000
Japan	[redacted]	N/A	[redacted]	N/A
United States	[redacted]			
Other Countries	12,052,000	[redacted]	1000	[redacted]
Global Totals	610,623,200	215,038,500	66 000[b]	23 000[b]

Abbreviation: N/A = not applicable.

[a] The EU countries represented here are Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

[b] Global total may not sum due to independent rounding.

Note: U-200 formulation is not marketed in Japan.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Lilly has not observed potential for misuse of insulin lispro for illegal purposes in completed clinical trials. The potential for misuse of insulin lispro for illegal purposes is not considered a risk, particularly in the absence of any associated euphoric or other central nervous system effects associated with addictive behaviour. Insulins, as a class, are not known to produce dependence syndromes (defined in the International Classifications of Diseases, Version 10 F19.20) [WHO 1999].

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not the initial RMP.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not the initial RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

None.

Severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application, is being removed as an important potential risk for the Tempo Pen based on the PRAC assessment report (endorsed on 29 September 2022).

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable, as there are no Important Identified Risks and Important Potential Risks for insulin lispro at this time.

SVII.3.2 Presentation of the Missing Information

Not applicable, as there is no missing information for insulin lispro at this time.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Other forms of routine pharmacovigilance activities for safety concerns:

1. Adverse events/product complaints

On a monthly basis, the adverse event (AE)/product complaint (PC) committee reviews AEs to detect increased frequency trends potentially related to lot-specific PCs. The AE/PC databases are queried and reviewed for potential drug-event combinations (DECs) that might indicate a manufacturing-related event. Any such DECs or trends would be further reviewed by a safety physician and other personnel, as indicated.

2. Potential change in the incidence of hypersensitivity, immunogenicity, or Lack of Drug Effect (LODE) with the manufacturing change (oKPB)

Humalog

Concerns initially arose about the potential risks of hypersensitivity and antigenicity due to the transition of patients to insulin lispro manufactured using the new manufacturing process (sKPB). These concerns were based on the identification of product-related impurities (insulin variants) associated with the sKPB process and a slightly increased concentration of high molecular weight forms.

Taking into account the scientific evidence, Lilly considers the likelihood of any untoward events related to these changes in manufacturing to be very low. For a limited time, routine and additional pharmacovigilance activities were put in place to monitor changes in the reporting of AEs related to hypersensitivity, immunogenicity, and lack of drug effect. However, at this time, all proposed analyses are considered routine.

Lilly allowed a maximum period of 6 months for the changeover from insulin lispro products manufactured using the current manufacturing process to products manufactured using sKPB.

On a monthly basis, a lot-specific AE review and analysis is performed for a 1-month period to identify potential events that might point to an unsuspected relationship to the Humalog manufacturing changes (oKPB). A standalone side-by-side analysis was conducted every 6 months, with an annual 12-month summary review, which was submitted to the agency as an annual analysis summary report. This occurred for a 2-year period beginning when the first batch of the proposed process was released for distribution and patient use (March 2019). Drug-event combinations from the 6-month reviews that might point to a manufacturing change event after appropriate signal analysis and clarification would have been provided to the relevant regulatory authority within 15 days of completion.

During the 2-year postmarketing commitment, there were no signals nor safety concerns identified for insulin lispro products manufactured using the oKPB process. Insulin lispro batches will continue to be monitored on a monthly basis via AE/PC surveillance activities as a component of Lilly's routine pharmacovigilance. The lot-specific analyses have been discontinued, and the final report has been submitted as part of the oKPB surveillance programme. As no issues were detected in this final analysis, the MAH now considers this commitment complete.

Given the lack of safety concerns identified in the postmarketing analyses for Humalog and the similarity between the 2 formulations, the MAH proposes to discontinue monitoring of events related to hypersensitivity, local injection site reactions, and immunogenicity; lack of drug effect (LODE); and increased drug effect and hypoglycaemia for all presentations of insulin lispro, including Lyumjev.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures are in place to manage the established safety profile and established risks as included in the Summary of Product Characteristics (SmPC).

V.2 Additional Risk Minimisation Measures

None

V.3 Summary of Risk Minimisation Measures

Routine risk minimisation as included in the SmPC.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Humalog/Liprolog and Lyumjev (Insulin Lispro)

This is a summary of the risk management plan (RMP) for Humalog/Liprolog and Lyumjev. The RMP details important risks of Humalog/Liprolog and Lyumjev, how these events can be minimised, and how more information will be obtained about Humalog/Liprolog's and Lyumjev's risks.

Humalog/Liprolog's and Lyumjev's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Humalog/Liprolog and Lyumjev should be used.

This summary of the RMP for Humalog/Liprolog and Lyumjev should be read in the context of all this 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 Humalog/Liprolog's and Lyumjev's RMP.

I - The Medicine and What It Is Used for

Humalog/Liprolog and Lyumjev are indicated for treatment of diabetes mellitus (see SmPC for the full indication). They contain insulin lispro as the active substance, and are given by subcutaneous injection, continuous subcutaneous insulin infusion (CSII), and intravenous use under medical supervision, depending on the pharmaceutical form and strength.

Further information about the evaluation of Humalog/Liprolog's and Lyumjev's benefits can be found in Humalog/Liprolog's and Lyumjev's EPAR, including in its plain-language summary, 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

Measures to minimise the risks identified for Humalog/Liprolog and Lyumjev include:

- 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.

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 safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks 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 Humalog/Liprolog and Lyumjev. 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).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None.
Missing information	None

II.B Summary of Important Risks

The safety information in the Product Information is aligned to the reference medicinal product.

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 Humalog/Liprolog or Lyumjev.

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

There are no studies required for Humalog/Liprolog or Lyumjev.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

None.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.