Confidential Information

EU Risk Management Plan (Version 6.1)

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

Approval Date: 26-Oct-2021 GMT

EU Risk Management Plan for Insulin human (INN or common name)

RMP version to be assessed as part of the application: Version 6.1

Data lock point for this RMP: 26 October 2020

Date of final sign off: See cover page of this document

Rationale for submitting an updated RMP:

- Align important identified/potential risks with those of other insulins.
- Routine pharmacovigilance activities regarding Methionine Arginine-Biosynthetic Human Insulin (MR-BHI), for all formulations of insulin human were completed.

Summary of significant changes in this RMP:

Routine pharmacovigilance activities regarding MR-BHI for all formulations of insulin human were completed. Severe hypoglycaemia was removed to align important identified/potential risks with those of other insulins.

Other RMP versions under evaluation

Not applicable

Details of the currently approved RMP

Version number: 5.1

Approved with procedure: UK/H/0030/062-070/IB/141

Date of approval (opinion date): 18 April 2018

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 human
Pharmacotherapeutic group(s) (ATC Code)	HUMULIN® S: A10A B01 HUMULIN® I: A10A C01 HUMULIN® M3: A10A D01
Marketing Authorisation Holder	Eli Lilly and Company
Medicinal products to which this RMP refers	HUMULIN S HUMULIN I HUMULIN M3 Note: The Humulin names outlined above are the names approved in the previous reference member state (United Kingdom). There are several variants of the Humulin name approved throughout Europe.
Invented name(s) in the European Economic Area (EEA)	UMULINE RAPIDE, UMULINE NPH, UMULINE PROFIL 30

Marketing authorisation procedure	The countries that follow the Mutual Recognition Procedure are as follows: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and United Kingdom. Procedure numbers: Humulin S vial FR/H/0645/001/ Humulin I vial FR/H/0645/002/ Humulin M3 vial FR/H/0645/003/ Humulin S cartridges FR/H/0645/004/ Humulin I cartridges FR/H/0645/005/ Humulin M3 cartridges FR/H/0645/006/ Humulin S Pen, KwikPen FR/H/0645/007/ Humulin I Pen, KwikPen FR/H/0645/008/ Humulin M3 Pen, KwikPen FR/H/0645/009/ Other EU country for which the products are approved under National Procedure is Poland
Brief description of the product	**Chemical class: peptide** Insulin human is human insulin produced from *Escherichia coli* by rDNA technology. [redacted]
	Summary of mode of action: The prime activity of insulin is the regulation of glucose metabolism. In addition, insulin has 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. • HUMULIN S is a short-acting insulin preparation. • HUMULIN I is an intermediate-acting insulin preparation. • HUMULIN M3 is a mixture of short-acting (30%) and intermediate-acting (70%) insulin preparation.

	Important information about its composition: A volume of 1 mL contains 100 IU human insulin (produced in *E coli* by rDNA technology). HUMULIN S vial, cartridge, and KwikPen: • One vial contains 10 mL equivalent to 1000 IU of soluble insulin. • One cartridge contains 3 mL equivalent to 300 IU of soluble insulin. • One prefilled pen contains 3 mL equivalent to 300 IU of soluble insulin. List of excipients: *m*-cresol, glycerol, water for injections, hydrochloric acid, and/or sodium hydroxide may be used to adjust pH. HUMULIN I vial, cartridge, and KwikPen: • One vial contains 10 mL equivalent to 1000 IU of isophane insulin. • One cartridge contains 3 mL equivalent to 300 IU of isophane insulin. • One prefilled pen contains 3 mL equivalent to 300 IU of isophane insulin. List of excipients: *m*-cresol, glycerol, phenol, protamine sulphate, dibasic sodium phosphate $7H_2O$, zinc oxide, water for injections, hydrochloric acid, and/or sodium hydroxide may be used to adjust pH. HUMULIN M3 vial, cartridge, and KwikPen: • One vial contains 10 mL equivalent to 1000 IU of biphasic isophane insulin – 30% soluble insulin/70% isophane insulin. • One cartridge contains 3 mL equivalent to 300 IU of biphasic isophane insulin – 30% soluble insulin/70% isophane insulin. • One prefilled pen contains 3 mL equivalent to 300 IU of biphasic isophane insulin – 30% soluble insulin/70% isophane insulin. List of excipients: *m*-cresol, glycerol, phenol, protamine sulphate, dibasic sodium phosphate $7H_2O$, zinc oxide, water for injections, hydrochloric acid, and/or sodium hydroxide may be used to adjust pH.
Hyperlink to the Product Information	See Module 1.3.1
Indication(s) in the EEA	**Current:** For the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis.
	Proposed: Not applicable

Dosage in the EEA	**Current:** The dosage should be determined by the physician, according to the requirement of the patient. HUMULIN S should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. It may also be administered intravenously. HUMULIN I and HUMULIN M3 should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. These formulations should not be administered intravenously. Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month. Care should be taken when injecting any HUMULIN insulin preparations to ensure that the insulin dies not enter the blood vessel. After any insulin injection, the injection site should not be massaged. Patients must be educated to use proper injection techniques. HUMULIN I (Isophane) may be administered in combination with HUMULIN S (Soluble) (see 'Instructions for use and handling' for 'Mixing of insulins'). HUMULIN M3 formulation is a ready-made defined mixture of soluble and isophane insulin designed to avoid the need for the patient to mix insulin preparations. A patient's treatment regimen should be based on his/her individual metabolic requirements.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	**Current:** HUMULIN S: A solution for injection in a cartridge or vial. HUMULIN S is a sterile, clear, colourless, aqueous solution of human insulin. • HUMULIN S (Soluble) 100 IU/mL solution for injection in vial • HUMULIN S (Soluble) 100 IU/mL solution for injection in cartridge • HUMULIN S KwikPen (Soluble) 100 IU/mL solution for injection HUMULIN I: A suspension for injection in a cartridge, vial, or prefilled pen. HUMULIN I is a sterile suspension of a white, crystalline precipitate of isophane human insulin in an isotonic phosphate buffer. • HUMULIN I (Isophane) 100 IU/mL suspension for injection in vial • HUMULIN I (Isophane) 100 IU/mL suspension for injection in cartridge • HUMULIN I KwikPen (Isophane) 100 IU/mL suspension for injection HUMULIN M3: A suspension for injection in a cartridge, vial, or prefilled pen. HUMULIN M3 is a sterile suspension of human insulin in the proportion of 30% soluble insulin to 70% isophane insulin. • HUMULIN M3 (Mixture 3) 100 IU/mL suspension for injection in vial • HUMULIN M3 (Mixture 3) 100 IU/mL suspension for injection in cartridge • HUMULIN M3 KwikPen (Mixture 3) 100 IU/mL suspension for injection
	Proposed: Not applicable

Product Overview

Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; EU = European Union; INN = International Nonproprietary Names; rDNA = recombinant DNA; 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). The World Health Organization (WHO) 2016 report on diabetes estimated that 422 million adults were living with diabetes in 2014 as compared to 108 million in 1980, reflecting the increased global prevalence of diabetes worldwide (4.7% to 8.5% [age-standardised] in the adult population) (WHO 2016 [WWW]).

SI.1.1 Incidence

Type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of all diabetes cases worldwide and shows wide variation, potentially due in part to geographic differences and environmental influences (Diabetes UK [WWW]; ADA 2009 [WWW]; Atkinson et al. 2014). Globally, the number of people with type 2 diabetes mellitus (T2DM) has more than doubled in the past 20 years (Zimmet et al. 2016). The incidence of diabetes (type 1 and 2 combined) in the US adults (aged 20 to 79 years) doubled from 3.2 per 1000 people in 1990 to 7.1 per 1000 people in 2012 (Geiss et al. 2014). Additionally, in the UK, Sharma et al. (2016) reported an increased T2DM incidence among both men and women during the period 2000 to 2013 (3.69 versus 3.99 per 1000 person-years at risk in men; 3.06 versus 3.73 per 1000 person-years at risk in women).

SI.1.2 Prevalence

The prevalence of diabetes (type 1 and 2) has been increasing over time as evidenced by Geiss et al. (2014) in which the prevalence per 100 persons was 3.5 in 1990 versus 7.9 in 2008 versus 8.3 in 2012. Overall, the global prevalence of diabetes mellitus (DM) regardless of type in adults (aged 20 to 79 years) in 2019 was estimated to be 463 million people (IDF 2019).

Worldwide, the prevalence of T1DM 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 T2DM 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 T2DM in adults (age ≥18 years) in 2015 was 9.4% overall, including 25.2% of adults aged ≥65 years (CDC 2017b [WWW]). Moreover, the prevalence of T2DM 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).

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 2016).

Age

In the US during 2011 to 2014, the prevalence rates of diagnosed and undiagnosed diabetes increased with age as follows (CDC 2017a [WWW]): age 20 to 44, 4.0%; age 45 to 64, 16.6%; age ≥65, 26.3%. Type 1 diabetes mellitus accounts for approximately 91% of all diabetes cases in those <20 years of age (Diabetes UK 2012 [WWW]; Mayer-Davis et al. 2017). In the UK and the US, the peak age range for diagnosis of T1DM is between 9 and 14 years (Diabetes UK [WWW]). Incidence rates decline after puberty and appear to stabilise in young adulthood (Maahs et al. 2010). Nonetheless, while the majority of diabetes cases in the paediatric population are T1DM, the incidence of T2DM has been shown to be increasing among youth aged 10 to 19 years in the US (Mayer-Davis et al. 2017). The number of people with T2DM is growing rapidly worldwide. This rise is associated with a number of factors including a rise in the ageing populations (IDF 2015).

Gender

In paediatric cases, girls and boys are equally affected by T1DM, while more girls develop T2DM than boys (Diabetes UK [WWW]; Dabelea et al. 2014; Mayer-Davis et al. 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, 2013).

There are many risk factors associated with T2DM. According to WHO 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. The majority of cases are due to autoimmune destruction of the beta cells in the pancreas, although there are some forms of T1DM with unknown aetiology (ADA 2018). Successful management of T1DM requires a combination of frequent self-monitoring of blood glucose (BG) levels, attention to meal planning, nutrient intake, physical activity, self-care behaviours, and the initiation of insulin therapy. Insulin therapy is most commonly delivered by injection of synthetic human insulin or insulin analogues manufactured by recombinant DNA biotechnology, which has almost completely replaced the use of insulin derived from animal-sourced pancreas.

To survive, people with T1DM must have insulin delivered by injection or an insulin pump. Treatment options include multiple daily injections of rapid-acting insulin combined with a daily basal insulin or subcutaneous insulin infusion via an insulin pump (Heller et al. 2017).

Type 2 diabetes mellitus is characterised by a progressive loss of beta cell insulin secretion, often coupled with insulin resistance (IR). Treatment should include individualised diabetes self-management education and support (DSMES) within a standardised framework that includes medical nutrition therapy (MNT) smoking cessation, psychosocial care, and strategies for engaging in regular physical activity (ADA 2018). Metformin monotherapy should be started at

diagnosis, unless there are contraindications. If the glycosylated haemoglobin A1c (HbA1c) target is not reached at 3 months, then metformin should be combined with another antihyperglycaemic agent (ADA 2018) considering patient risk factors and access to medication. If the target HbA1c is not reached at 3 months with dual therapy, then another antihyperglycaemic agent with a different mechanism of action could be added with the goal to achieve glycaemic control while minimizing side effects. When initiating insulin, basal insulin is most convenient to initiate and may be added to 1 or 2 oral antihyperglycaemic agents. For patients with T2DM, if fasting BG levels are within range on basal insulin and oral antihyperglycaemic medications, but the A1C is not within target, a number of options are available. These include to discontinue oral medications with the exception of metformin, continue on basal insulin, and add a more rapid-acting insulin at one or more mealtimes. Other options include basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), initiating premixed (biphasic) insulin twice daily, or a premixed insulin analogue 3 times daily. At all times, treatment changes or intensification should be closely monitored to obtain pattern control with tolerability and safety. For patients that require a large amount of insulin to maintain glycaemic control, concentrated insulins should be considered to less the burden of frequent injections and achieve glycaemic control and patient adherence (ADA 2018).

For patients with T2DM, there are numerous oral antihyperglycaemic medications and noninsulin injectable agents available to lower BG levels (Tahrani et al. 2016). Since these therapies act through different biological mechanisms, they do not directly affect the efficacy of insulin. These medications are not indicated for patients with T1D, who rely on insulin for survival. These alternative therapies can be used either alone or with other agents that act through a different biological mechanism, and some agents are approved for use with insulin. All of the agents listed below are administered orally, except for GLP-1 RAs, which are injected.

- **Metformin,** a biguanide, is usually the first agent prescribed to newly diagnosed patients with T2DM. It acts to lower BG through cellular insulin signalling to improve insulin uptake in muscle cells and decrease liver glucose production. Benefits of metformin include absence of hypoglycaemia, associated weight loss and low cost, while risks include lactic acidosis and diarrhoea. Patients with chronic kidney disease cannot use metformin (Tahrani et al. 2016, pg 569).
- **Sulphonylureas** (for example, glyburide, glipizide) act through cellular receptors on pancreatic beta cells to promote insulin release. Risks of sulphonylureas include hypoglycaemia (low blood sugar) and weight gain (Tahrani et al. 2016, pg 569).
- **Meglitinides** have a similar mechanism of action and risks as sulphonylureas, with faster onset and shorter duration of actions (Tahrani et al. 2016, pg 569).
- **Alpha-glucosidase inhibitors** inhibit enzymes in intestinal wall cells to delay carbohydrate digestion and absorption, which in turn reduces BG excursions and lowers insulin levels at mealtime. Alpha-glucosidase inhibitors are widely used in Asian patients who have a carbohydrate-rich diet, but can produce abdominal discomfort and flatulence (Tahrani et al. 2016, pg 569).

- **Thiazolidinediones (TZDs)** (pioglitazone, rosiglitazone) bind to a nuclear receptor in fat, muscle, liver, and pancreatic beta cells to promote insulin sensitivity, glucose uptake, and fat formation. Risks of TZDs include oedema, weight gain, and increased risk of bone fractures (Tahrani et al. 2016, pg 569).
- **Dipeptidyl peptidase-4 (DPP-4)** is an enzyme that inactivates endogenous GLP-1. **Dipeptidyl peptidase-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 and decreases BG. Dipeptidyl peptidase-4 inhibitors have a very low incidence of gastrointestinal effects and hypoglycaemia (Tahrani et al. 2016, pg 569).
- **Sodium glucose co-transporter-2 inhibitors** (for example, empagliflozin, canagliflozin) promote urinary glucose excretion, which lowers BG by inhibiting an enzyme, which acts to reabsorb glucose from the kidney tubules. An increased risk of genitourinary infections, especially in female patients, may occur with these oral agents (Tahrani et al. 2016, pg 570).
- **Glucagon-like peptide-1 receptor agonist**s (for example, dulaglutide, liraglutide, semaglutide) are noninsulin agents that act to lower BG levels by enhancing glucose-dependent insulin secretion by pancreatic beta cells, suppressing elevated glucagon secretion, and delaying gastric emptying, similar to endogenous GLP-1. Glucagon-like peptide-1 receptor agonists have an additional benefit of weight loss, but nausea, vomiting, and diarrhoea are often reported (Tahrani et al. 2016, pg 571).

All GLP-1 RAs are available as only injectable form except semaglutide, which is also approved for oral use.

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 [WWW]) with the greatest impact seen in countries with large adult populations like China, India, the US, and Brazil (Guariguata et al. 2014; IDF 2015). Furthermore, diabetes accounted for approximately 14.5% of global all-cause deaths among people 20 to 70 years of age (IDF 2015). 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 T1DM 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 T1DM (Diabetes UK 2012 [WWW]).

Type 2 diabetes mellitus reduces life expectancy up to 10 years (Diabetes UK 2012 [WWW]) 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 T2DM-related death is also related to age. In individuals with T2DM 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 T1DM 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 T1DM as their survival increases; accordingly, patients with T1DM have a 10 times higher risk for cardiovascular events such as myocardial infarction, stroke, angina, and the need for coronary-artery revascularization (Orchard et al. 2006; Atkinson et al. 2014).

Similarly, T2DM is associated with significant morbidity including macrovascular and microvascular complications (Shah et al. 2015). Cardiovascular disease is the leading complication and can include the following: peripheral arterial disease, heart failure, stable angina, nonfatal myocardial infarction, and stroke among others; approximately half of patients with T2DM 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 Comorbidities

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

Comorbidity	**Expected magnitude of comorbidity (prevalence)**	**Expected co-medications of comorbidity**
Obesity	DM: 74% Canada (Slater et al. 2011); T1DM: 12.6% youth Germany (Go et al. 2014) T2DM: 79.4% youth Germany (Go et al. 2014); 29.5% UK (Girman et al. 2012); 31.13% southern Germany (Boehme et al. 2015)	Weight loss drugs, lipase inhibitors, appetite suppressants
Cardiovascular Disease		
Myocardial Infarction	Sweden: 2.4% T1DM and 9.1% T2DM (Rawshani et al. 2017)	vasodilators, cardiac depressant drugs, antiarrhythmic drugs, antithrombotic drugs, thrombolytic drugs

Stroke	Sweden: 1.6% T1DM and 6.6% T2DM (Rawshani et al. 2017)	antihypertensives, anticoagulants, antiplatelets
Coronary Heart Disease	Sweden: 4.7% T1DM and 17.3% T2DM (Rawshani et al. 2017)	cholesterol-modifying medications, beta blockers, aspirin, calcium channel blockers, ranolazine, nitroglycerin, ACE inhibitors, and angiotensin II receptor blockers
Heart Failure	Sweden: 1.5% T1DM and 6.7% T2DM (Rawshani et al. 2017)	diuretics, vasodilators, cardiostimulatory/inotropic drugs, cardioinhibitory drugs
Hypertension	Finland: 15.2% T1DM <30years of age (Reunanen et al. 2000) Italy: 66.6% T2DM (Colivicchi et al. 2007) Germany: 77.0% T2DM age- and sex-standardised (Boehme et al. 2015)	beta blockers, calcium channel blockers, ACE inhibitors and angiotensin II receptor blockers, direct renin inhibitors, diuretics
Hyperlipidaemia	US: LDL >100 mg/dL without treatment, T2DM: 28% (Brandle et al. 2003); 93.5% (Mody et al. 2007) T2DM patients receiving cholesterol medication: 30% (Brandle et al. 2003) LDL-C level >130 mg/dL, T1DM patients: 15%; T2DM patients: 24% (Kershnar et al. 2006)	lipid-modifying medications
Nephropathy/Microalbuminuria	Nephropathy EU, T1DM: 30.5% (Toeller et al. 1999) Microalbuminuria EU, T1DM: 8.8% (Toeller et al. 1999 Sweden: 7.7% T1DM and 8.5% T2DM (Rawshani et al. 2017) End-Stage Kidney Disease Sweden: 1.2% T1DM and 0.2% T2DM (Rawshani et al. 2017)	ACE inhibitors and angiotensin II receptor blockers
Retinopathy	EU: 46.7% T1DM (Toeller et al. 1999) Scotland: 32.5% (Ding et al. 2010)	VEGF inhibitors, corticosteroids, ophthalmics
Neuropathy	UK: up to 50% of the DM population (Diabetes UK 2012 [WWW]); 26.4% T2DM (Davies et al. 2006)	antiseizure drugs, antidepressants
Sexual Dysfunction	Erectile Dysfunction Global Literature Review: 35% T1DM	PDE-5 inhibitors

	and 90% T2DM (Malavige and Levy 2009)	
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 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; T1DM = type 1 diabetes mellitus; T2DM = 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

Consistent with global regulatory standards of the day, pharmacology, pharmacokinetic, and toxicology studies with biosynthetic human insulin (BHI, LY041001) were performed in support of the original marketing authorisation of Humulin® in 1982. The biological activity of BHI has been evaluated in a wide variety of in vitro tests, all of which demonstrated that BHI and pancreatic human insulin were highly similar. The nonclinical pharmacological properties of BHI have been studied in numerous animal models, and BHI has now been used to treat millions of patients with diabetes. The hypoglycaemic potency of BHI was determined to be equivalent to purified pancreatic insulins as determined by the USP rabbit assay. Most of the pharmacological and toxicological actions of human insulin are related to interactions with the insulin receptor; the dose-limiting toxicity in both animals and humans is hypoglycaemia.

The most important conclusions from toxicology studies of BHI were as follows:

- The selection of dose levels of BHI for the single- and repeat-dose studies in rats, dogs, and monkeys was governed by the dose-limiting hypoglycaemic activity of BHI.
- The minimal lethal dose of BHI injected subcutaneously in rats and mice was >10 U/kg. This dose was a large multiple of the average preprandial therapeutic dose of BHI (0.3 to 0.6 U/kg/day) in patients with T2DM without severe IR.
- Dogs given a single subcutaneous injection of 2 U/kg/day or an intravenous (IV) injection of 0.1 U/kg of BHI exhibited hypoglycaemia and related pharmacological effects but no important off-target toxicity.
- No BHI-related toxic effects were observed when rats were given daily subcutaneous injections of 2.4 U/kg of BHI for 1 month at 4- to 8-fold the human dose. Similarly, beagle dogs given daily subcutaneous injections of 2 U/kg or IV injections of 0.1 U/kg of BHI for 1 month exhibited marked hypoglycaemia, but no adverse effects were seen on clinical pathology parameters. There were no target organ changes at 3- to 7-fold the human dose. There was no evidence of tissue damage or irritation at the site of injection in the rats or dogs.
- Biosynthetic human insulin was not genotoxic in the in vivo sister chromatid exchange assay and the in vitro gradient plate and unscheduled DNA synthesis assays.

Studies have shown that endogenous human insulin crosses the placenta in only minimal amounts. While there are no adequate and well-controlled studies in pregnant women, published literature demonstrates the maternal and foetal benefits of insulin treatment in patients with diabetes during pregnancy. Biosynthetic human insulin is identical to the endogenous human hormone; therefore, reproduction and developmental toxicity studies and carcinogenicity studies were not performed in animals.

Thus, it was concluded that injections of pharmacologically effective doses of BHI in animals did not produce toxic effects. Therefore, the nonclinical programme and 30 years of clinical use support the safety of HUMULIN for parenteral use in humans for the treatment of diabetes.

SII.2 Safety Pharmacology

Not applicable.

SII.3 Other Toxicity-Related Information or Data

Not applicable.

Module SIII - Clinical Trial Exposure

Table SIII.1. Duration of Humulin (LY041001) Exposure[a]

Cumulative for all indications (person time)		
Duration of exposure	**Patients (N)**	**Person time (years)[b]**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: [redacted]

Table SIII.2. Age Group and Gender[a]

Age group	Patients				Person time (years)[b]			
				Total				Total

Source:

Table SIII.3. Ethnic Origin[a]

Ethnic origin	Patients	Person time (years)[b]

Source:

Module SIV - Populations Not Studied in Clinical Trials

[redacted]

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

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

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

Due to the late stage in its life cycle and the vast real-world clinical experience with the product, knowledge of the safety profile of insulin human today exceeds the limitations of the clinical trial development programme.

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	Insulin human has been administered to millions of patients for many years. The MAH has no knowledge of rare conditions developing in conjunction with insulin human therapy.
Due to prolonged exposure	N/A	Insulin human has been administered to millions of patients for many years. The MAH has no knowledge of rare conditions developing due to prolong exposure of the drug.
Due to cumulative effects	N/A	Insulin human is identical to human insulin. There are no known cumulative effects.
Which have a long latency	N/A	Insulin human has been administered to millions of patients for many years. The MAH has no knowledge of any condition that develops after a long latency period with this drug.

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

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

Children

Insulin human (Humulin) is licensed in the EU for the treatment of patients with DM who require insulin for the maintenance of glucose homeostasis (Summary of Product Characteristics [SmPC]). This indication statement includes children and infants as well.

Until the 1990s when insulin analogues became available, insulin human, which is identical to endogenous insulin, was the predominantly used insulin for the treatment of diabetes. For this reason, it has also been widely used in children of all ages. It still is used as an essential component of most daily replacement regimens in many parts of the world (Galli-Tsinopoulou 2011).

The clinical efficacy and safety of insulin human in children have not been studied as extensively as in the adult population. This is particularly true for very young children (for example, infants and neonates). Although only 1 clinical trial has been conducted in a paediatric population, some early clinical trials with insulin human allowed enrolment of subjects younger than 18 years of age.

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 comorbidities, polypharmacy, and increased risk for adverse events (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 T2DM 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 are often excluded from clinical trials on insulin treatment, 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.

Pregnant or Breastfeeding Women

The marketing authorisation holder (MAH) has conducted a prospective, open-label, parallel study comparing the efficacy and safety of insulin human (n=20) versus animal-derived insulin (n=23) in 43 pregnant women with T1DM or T2DM from 10 to 20 weeks of gestation through to

delivery (Jovanovic-Peterson et al. 1992). Insulin human is not contraindicated for use in pregnancy. It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy (Kitzmiller et al. 2008). Insulin requirements usually decline during the first trimester and increase during the second and third trimesters.

Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet (SmPC).

Patients with Hepatic Impairment

Insulin requirements may change significantly in patients with hepatic impairment (SmPC). Study F3Z-MC-IOEK determined the influence of hepatic impairment on the pharmacokinetics and glucodynamics of insulin lispro and regular human insulin in patients with T2DM 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 BG excursion profiles of insulin lispro or regular human insulin.

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 insulin lispro and regular human insulin in 25 patients with T2DM 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.

Patients with Other Relevant Comorbidities

Insulin human treatment regimens and doses are adjusted for each individual patient to maintain normoglycaemia. Patients need to measure their BG regularly to calculate the correct number of insulin human units. There are no known other relevant comorbidities that would substantially affect pharmacokinetic/pharmacodynamic parameters, clinical risks, or benefits for insulin human.

Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

Therapy with insulin human is usually initiated when endogenous insulin is not present or is not present in sufficient amounts to overcome hyperglycaemia. The disease severity upon which insulin is introduced into therapy is well defined and is not different between clinical trials and clinical practice.

Subpopulations Carrying Known and Relevant Polymorphisms

Patients with severe IR require extremely large doses of insulin to maintain glycaemic control (Reutrakul et al. 2012). Among other causes, severe IR may be attributed to genetic defects of the insulin receptor gene that decreases insulin binding or to antibodies to the insulin receptor (Kahn et al. 1976). The MAH has not conducted any clinical trials on the use of insulin human in these subpopulations.

Patients of Different Racial and/or Ethnic Origin

Clinical trials of insulin human were conducted globally and included patients of different racial or ethnic backgrounds. Insulin human has been used in millions of patients over a long period of time. Its benefits have been established in patients of any racial or ethnic origin.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

[redacted]

SV.1.2 Exposure

[redacted]

Table SV.1. Exposure Table by Indication

[redacted]			

[a] Global totals may not sum due to independent rounding.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

The potential for misuse of insulin human for illegal purposes is not considered to be a significant 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 ICD10 F19.20).

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, 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, this is not the initial RMP.

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

Severe hypoglycaemia, classified as an important identified risk in the previous RMP, is removed from the list of safety concerns.

Justification of Removal

Severe hypoglycaemia with insulin human is well characterised, and is not subject to additional risk minimisation activities. Hypoglycaemia is readily detectable, and healthcare professionals have a high level of knowledge regarding the risk. Management of blood glucose is a primary focus of diabetes management, and is not a new practice for patients or healthcare providers. Given the widespread awareness, the risk can be appropriately managed in clinical practice through routine risk minimisation measures. This is to maintain consistentcy with other insulins.

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

Important Identified Risk: Not Applicable

Important Potential Risk**:** Not Applicable

SVII.3.2 Presentation of the Missing Information

Missing Information: Not applicable

Table SVIII.1

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risk	None
Important potential risk	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:

Routine **follow-up** will be conducted on events of special interest.

Other forms of routine pharmacovigilance activities

On a monthly basis, the 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 (DEC) 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.

III.2 Additional Pharmacovigilance Activities

1Not Applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

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

V.1 Routine Risk Minimisation Measures

1Routine Risk Minimisation as included in the SmPC.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

3Routine risk minimisation as included in the SmPC.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Humulin (Insulin Human)

This is a summary of the RMP for Humulin. The RMP details important risks of Humulin, how these risks can be minimised, and how more information will be obtained about Humulin's risks and uncertainties (missing information).

Humulin's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Humulin should be used.

Important new concerns or changes to the current ones will be included in updates of Humulin's RMP.

I - The Medicine and What It Is Used for

Humulin is authorised for the treatment of patients with DM who require insulin for the maintenance of glucose homeostasis. It contains insulin human as the active substance, and it is given by subcutaneous route of administration.

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Humulin is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Humulin 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 Humulin. 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 (for example, on the long-term use of the medicine).

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

II.B Summary of Important Risks

Not applicable

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 Humulin.

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

Not applicable

Part VII: Annexes

Annex **Page**

Annex 1 - EudraVigilance Interface

Annex 2 - Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Table 1. Annex II: Planned and Ongoing Studies

None

Table 2. Annex II: Completed Studies

Study	Summary of Objectives	Safety Concerns Addressed
[redacted]	[redacted]	[redacted]

[redacted]

Annex 3 - Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Table of Contents

Part	Title
Part A	None
Part B	None
Part C	None

Part A: Requested Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review with this Updated Version of the RMP

None.

Part B: Requested Amendments of Previously Approved Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review with this Updated Version of the RMP

None.

Part C: Previously Agreed Protocols for Ongoing Studies and Final Protocols Not Reviewed by the Competent Authority

None

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not Applicable

Annex 5 - Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

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

Not applicable.

Annex 7 - Other Supporting Data (including referenced material)

[ADA] American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2009;32(suppl 1):S62-S67.

[ADA] American Diabetes Association. Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(suppl 1).

Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383(9911):69-82.

Ballotari P, Vincentini M, Manicardi V, Gallo M, Chiatamone Ranieri S, Greci M, Giorgi Rossi P. Diabetes and risk of cancer incidence: results from a population-based cohort study in northern Italy. *BMC Cancer*. 2017;17(1):703.

Barone BB, Yeh H-C, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*. 2008;300(23):2754-2764.

Boehme MW, Buechele G, Frankenhauser-Mannuss J, Mueller J, Lump D, Boehm BO, Rothenbacher D. Prevalence, incidence and concomitant co-morbidities of type 2 diabetes mellitus in South Western Germany--a retrospective cohort and case control study in claims data of a large statutory health insurance. *BMC Public Health*. 2015;15:855.

Borchers AT, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. *Autoimmun Rev*. 2010;9(5):A355-A365.

Brandle M, Zhou H, Smith BR, Marriott D, Burke R, Tabaei BP, Brown MB, Herman WH. The direct medical cost of type 2 diabetes. *Diabetes Care*. 2003;26(8):2300-2304.

Briscoe VJ, Davis SN. Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology, and management. *Clin Diabetes*. 2006;24(3):115-121.

Cancer Research UK. Cancer incidence by age. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero. Updated June 2018. Accessed April 27, 2018.

Carstensen B, Jorgensen ME, Friis S. The Epidemiology of Diabetes and Cancer. Curr Diab Rep (2014) 14:535

[CDC] Centers for Disease Control and Prevention. Health, United States, 2016. Available at: https://www.cdc.gov/nchs/data/hus/hus16.pdf. Published May 2017a. Accessed October 02, 2017.

[CDC] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017: estimates of diabetes and its burden in the United States. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Published 2017b. Accessed October 02, 2017.

[CDC] Centers for Disease Control and Prevention. National diabetes fact sheet, 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. 2011. Accessed September 22, 2014.

[CDC] Centers for Disease Control and Prevention. National Surveillance Data. Available at: https://www.cdc.gov/nchs/data/hus/hus13.pdf. Published 2013. Accessed September 18, 2018.

[CDC] Centers for Disease Control and Prevention. 2013. National Surveillance Data. Available at http://apps.nccd.cdc.gov/DDTSTRS/NationalSurvData.aspx. Accessed 15 February 2013.

Colhoun HM, SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia*. 2009;52:1755-1765.

Colivicchi F, Uguccioni M, Ragonese M, Nardozi C, Angotti S, Principe F, Pinto SL, Santini M. Cardiovascular risk factor control among diabetic patients attending community-based diabetic care clinics in Italy. *Diabetes Res Clin Pract*. 2007;75(2):176-183.

Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26(6):1902-1912.

Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;52:1766-1777.

Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*. 2014;311(17):1778-1786.

Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29(7):1518-1522.

Diabetes UK. Facts & figures. Available at: https://www.diabetes.org.uk/Professionals/Position-statements-reports/Statistics. Accessed September 29, 2017.

Diabetes UK. Key statistics on diabetes. Available at: http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf. Published April 2012. Accessed September 7, 2018.

Ding J, Strachan MW, Reynolds RM, Frier BM, Deary IJ, Fowkes FG, Lee AJ, McKnight J, Halpin P, Swa K, Price JF; Edinburgh Type 2 Diabetes Study Investigators. Diabetic retinopathy and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Mellitus Study. *Diabetes*. 2010;59(11):2883-2889.

Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese PG. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabetic Med.* 2005;22(6):749-755.

[EMA] European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. Anti-diabetes medication to be taken off the market. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf. Published September 2010. Accessed September 7, 2018.

Fineberg SE, Galloway JA, Fineberg NS, Goldman J. Effects of species of origin, purification levels, and formulation on insulin immunogenicity. *Diabetes*. 1983;32(7):592-599.

Fineberg SE, Galloway JA, Fineberg NS, Rathbun MJ. Immunologic improvement resulting from the transfer of animal insulin-treated diabetic subjects to human insulin (recombinant DNA). *Diabetes Care*. 1982;5(suppl 2):107-113.

Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH Jr. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care*. 2003;26(1):89-96.

Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol*. 2014;10(12):711-722.

Galli-Tsinopoulou A. Insulin therapy in children and adolescents with diabetes. *Diabetes Res Clin Prac*. 2011;93(suppl 1):S114-S117.

Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, Albright AL, Gregg EW. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. *JAMA*. 2014;312(12):1218-1226.

Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33(7):1674-1685.

Girman CJ, Kou TD, Brodovicz K, Alexander CM, O'Neill EA, Engel S, Williams-Herman DE, Katz L. Risk of acute renal failure in patients with type 2 diabetes mellitus. *Diabet Med*. 2012;29(5):614-621.

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.

Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010;304:411-418.

Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149.

Handelsman Y, Leroith D, Bloomgarden ZT, Dagogo-Jack S, Einhorn D, Garber AJ, Grunberger G, Harrell RM, Gagel RF, Lebovitz HE, McGill JB, Hennekens CH. Diabetes and cancer--an AACE/ACE consensus statement. *Endocr Pract*. 2013;19(4):675-693.

Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. *Diabetes Care*. 2014;37(9):2579-2586.

Heinemann L, Linkeschova R, Klaus R, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care*. 2000;23:644-649.

Heller S, Amiel S, Campbell M, Choudhary P, Cooper C, Dimairo M, Elliott J, Hammond P, Lee E, Lindsay R, Mansell P, Waugh N, White D. Relative effectiveness of insulin pump treatment

over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). *BMJ*. 2017;356:j1285.

Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia*. 2009;52:1732-1744.

Holden SE, Jenkins-Jones S, Morgan CL, Peters JR, Schernthaner G, Currie CJ. Prevalence, glucose control and relative survival of people with type 2 diabetes in the UK from 1991 to 2013. *Diabet Med*. 2017;34(6):770-780

[ISMP] List of high-alert medications in acute care settings. Available at: https://www.ismp.org/sites/default/files/attachments/2018-08/highAlert2018-Acute-Final.pdf Accessed September 18, 2018.

[IDF 2015] International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.

[IDF 2019] International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019. Accessed September 17, 2021. Available at: https://www.diabetesatlas.org

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes.. *Diabetes Care*. 2015;38(1):140-149.

Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. *Diabetologia*. 2009;52:1745-1754.

Jovanovic-Peterson L, Kitzmiller J, Peterson C. Randomized trial of human versus animal species insulin in diagetic pregnant women: improved glycemic control, not fewer antibodies to insulin, influences birth weight. *Am J Obstet Gynecol*. 1992;167(5):1325-1330.

Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N Engl J Med*. 1976;294(14):739-745.

Kershnar AK, Daniels SR, Imperatore G, Palla SL, Petitti DB, Pettitt DJ, Marcovina S, Dolan LM, Hamman RF, Liese AD, Pihoker C, Rodriguez BL. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *J Pediatr*. 2006;149(3):314-319.

Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, Gunderson EP, Herman WH, Hoffman LD, Inturrisi M, Jovanovic LB, Kjos SI, Knopp RH, Montoro MN, Ogata ES, Paramsothy P, Reader DM, Rosenn BM, Thomas AM, Kirkman MS. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care*. 2008;31(5):1060-1079.

Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am*. 2010;39(3):481-497.

Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. *J Sex Med*. 2009;6(5):1232-1247.

Mannucci E. Insulin therapy and cancer in type 2 diabetes. *ISRN Endocrinol*. 2012;2012:240634.

Mannucci E, Cremasco F, Romoli E, Rossi A. The use of insulin in elderly patients with type 2 diabetes mellitus. *Expert Opin Pharmacother*. 2011;12(18):2865-2881.

Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med*. 2017;376(15):1419-1429.

Mianowska B, Szadkowska A, Pietrzak I, Zmysłowska A, Wegner O, Tomczonek J, Bodalski J, Młynarski W. Immunogenicity of different brands of human insulin and rapid-acting insulin analogs in insulin-naive children with type 1 diabetes. *Pediatr Diabetes*. 2011;12(2):78-84.

Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R, Pawar V. Economic impact of cardiovascular co-morbidity in patients with type 2 diabetes. *J Diabetes Complications*. 2007;21(2):75-83.

Mooradian AD. Special considerations with insulin therapy in older adults with diabetes mellitus. *Drugs Aging*. 2011;28(6):429-438.

Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society. *J Am Geriatr Soc*. 2013;61(11):2020-2026.

Moyes V, Driver R, Croom A, Mirakian R, Chowdhury TA. Insulin allergy in a patient with Type 2 diabetes successfully treated with continuous subcutaneous insulin infusion. *Diabet Med*. 2006;23(2):204-206.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513-1530.

Nissen SE, Wolski K. Rosiglitazone revisited. An updated meta analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med*. 2010;170:1191-1201.

Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. *Diabetes Care*. 2006;29(11):2528-2538.

ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais, GR, Diaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328.

Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, Seaquist ER, Ismail-Beigi F, Sullivan MD, Lovato LC, Bergenstal RM, Gerstein HC; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.

Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376(15):1407-1418.

Read SH, Kerssens JJ, McAllister DA, Colhoun HM, Fischbacher CM, Lindsay RS, McCrimmon RJ, McKnight JA, Petrie JR, Sattar N, Wild SH; Scottish Diabetes Research Network Epidemiology Group. Trends in type 2 diabetes incidence and mortality in Scotland between 2004 and 2013. *Diabetologia*. 2016;59(10):2106-2113.

Reunanen A, Kangas T, Martikainen J, Klaukka T. Nationwide survey of comorbidity, use, and costs of all medications in Finnish diabetic individuals. *Diabetes Care*. 2000;23(9):1265-1271.

Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: review and metaanalysis. *J Diabetes Sci Technol*. 2012;6(2):412-420.

Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care*. 2005;28(9):2130-2135.

Schütt M, Fach EM, Seufert J, Kerner W, Lang W, Zeyfang A, Welp R, Holl RW; DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Multiple complications and frequent severe hypoglycaemia in ‘elderly’ and ‘old’ patients with type 1 diabetes. *Diabet Med*. 2012;29(8):e176-e179.

Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care*. 2013;36(5):1384-1395.

Selvin E, Parinello CM, Daya N, Bergenstal RM. Trends in insulin use and diabetes control in the U.S.: 1988–1994 and 1999–2012. *Diabetes Care* 2016;39:e33-e35.

Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol*. 2015;3(2):105-113.

Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open*. 2016;6(1):e010210.

Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. *Cancer Sci*. 2013;104(1):9-14.

Slater M, Perruccio AV, Badley EM. Musculoskeletal comorbidities in cardiovascular disease, diabetes and respiratory disease: the impact on activity limitations; a representative population-based study. *BMC Public Health*. 2011;11:77.

Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia*. 2009;52:1699-1708.

Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2016;12(10):566-592.

Tennagels N, Werner U. The metabolic and mitogenic properties of basal insulin analogues. *Arch Physiol Biochem*. 2013;119(1):1-14.

Toeller M, Buyken AE, Heitkamp G, Berg G, Scherbaum WA. Prevalence of chronic complications, metabolic control and nutritional intake in type 1 diabetes: comparison between different European regions. EURODIAB Complications Study group. *Horm Metab Res*. 1999;31(12):680-685.

van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil*. 2010;17(suppl 1):S3-S8.

Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr Relat Cancer*. 2009;16(4):1103-1123.

[WHO] World Health Organization. Global report on diabetes. Available at: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Published 2016. Accessed September 29, 2017.

Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol*. 2016;12(10):616-622.

Zucker I, Shohat T, Dankner R, Chodick G. New onset diabetes in adulthood is associated with a substantial risk for mortality at all ages: a population based historical cohort study with a decade-long follow-up. *Cardiovasc Diabetol*. 2017;16(1):105.

Annex 8 - Summary of Changes to the Risk Management Plan Over Time

Version	Approval date Procedure	Change
1	20 October 2013 Procedure: UK/H/030/12, 22, 25, 28, 29, 32, 48, 49, 52/X/109/G	Initial RMP
2	06 February 2014 Procedure: UK/H/030/12, 22, 25, 28, 29, 32, 48, 49, 52/X/109/G	Updates for clinical trial exposure, post-authorisation experience, EU requirements, summary of safety concerns, and RMP summary.
3	23 May 2014 Procedure: UK/H/030/12, 22, 25, 28, 29, 32, 48, 49, 52/X/109/G	Updates to the pharmacovigilance plan in response to regulatory feedback on [redacted]. Change to MedDRA version 17.0.
4	11 July 2015 Procedure: UK/H/0030/062-070/IB/141	Updates to the pharmacovigilance activity status and post-authorisation development plan.
5	20 September 2016 Procedure: MA 00006/0689 (withdrawn)	Updates for the submission of U-500 in the UK, Postmarketing exposure, clinical trial exposure, trial status, and pharmacovigilance descriptions.
5.1	12 October 2018 Procedure: UK/H/0030/062-070/IB/141	Conversion to the GVP Module V (Rev 2) format [Safety concerns] Important identified risk of *hypoglycaemia* changed to *severe hypoglycaemia* Removal of *hypersensitivity* as important identified risk Removal of *Oedema leading to CHF when insulin human is used concomitantly with TZDs* as important identified risk Removal of *medication errors* as important potential risk (incorporated into *severe hypoglycaemia* as the outcome) Removal of *antigenicity* as important potential risk Removal of *neoplasms* as important potential risk.

6.1	See Cover Page	Module SI: Minor data in epidemiology of the indications and target populations was updated with recent data. Module SI.1.4: Under the bullet point "Glucagon-like peptide-1 receptor agonist", text has been added to specify the dosage forms of GLP-1 RA. Module SIII: Table footnotes added in Tables SIII.1, 2, and 3. Module SV: Post-authorisation experience was updated with most recent exposure data. Important identified risk of severe hypoglycaemia was removed and justification for removal of important identified risk of severe hypoglycaemia was updated in Module SVII – identified and potential risks. Part III: Routine pharmacovigilance activities regarding MR-BHI for all formulations of insulin human were completed. Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities) was updated, as severe hypoglycaemia was removed and MR-BHI was completed. Annex 2, Annex 3, and Annex 4 were updated, as MR-BHI was completed.

Abbreviations: CHF = congestive heart failure; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; [redacted]; RMP = risk management plan; TZD