EU Risk Management Plan (Version 5.1)

Global Patient Safety
Signatory information is available on request.
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EU Risk Management Plan for Insulin human (INN or common name)

RMP version to be assessed as part of the application: Version 5.1

Data lock point for this RMP: June 30, 2018

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Rationale for submitting an updated RMP:

Update to new EU format for the RMP

Summary of significant changes in this RMP:

Conversion to the GVP Module V (Rev 2) format

Adverse Drug Reactions previously classified as risks, removed from the list of safety concerns.

Other RMP versions under evaluation

Not applicable.

Details of the currently approved RMP

Version number: 4

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

Date of approval: 20/04/2018

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.

Table of content

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 2015 was estimated to be 8.8% (IDF 2015; Ogurtsova et al. 2017).

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 injectable 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).

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	Weight loss drugs, lipase inhibitors, appetite suppressants

	(Go et al. 2014); 29.5% UK (Girman et al. 2012); 31.13% southern Germany (Boehme et al. 2015)	
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	ACE inhibitors and angiotensin II receptor blockers

	(Rawshani et al. 2017)	
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 and 90% T2DM (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 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

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

Table SIII.2. Age Group and Gender

Age group	Patients				Person time (years)[a]			
[redacted]								

Table SIII.3. Ethnic Origin

Ethnic origin	Patients (N = 50,114)	Person time (years)[a]
[redacted]		

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

Cumulative patient exposure reported through 30 June 2018 totals approximately 78.5 million patient-years of insulin human (373,000 patient-years for Humulin R U-500 and 78.2 million patient-years for all other formulations).

[redacted]

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

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

Justification of Removal:

Recombinant human insulin preparations have a lower incidence of immune response than animal-derived insulins, and clinically observable allergic phenomena have become very rare (Fineberg et al. 2003). In general, hypersensitivity reactions to insulin products occur in around 0.5% of insulin users (Moyes et al. 2006). In the clinical development programme, the frequency of hypersensitivity in Humulin was observed to be less than 1/10,000 and was characterised as a very rare event (SmPC Humulin).

In the postmarketing setting, cumulatively through 30 June 2018, hypersensitivity has been reported at an incidence of 0.01% based on an estimated patient exposure to insulin human of 78.5 million patient-years of insulin human. The incidence of hypersensitivity with clinically significant outcome such as anaphylaxis is very rarely reported.

Hypersensitivity (systemic allergy) is described as an adverse drug reaction (ADR) in the SmPC and is followed up via routine pharmacovigilance, namely, through signal detection and adverse reaction reporting. This ADR does not require further characterisation. The revision to GVP Module 5 (Rev 2), published in March 2017, has not only clarified that not all ADRs are risks but also that an important risk is one for which the undesirable clinical outcome of the ADR has (or could have) an impact on benefit risk. Hypersensitivity does not have an impact on the risk-benefit profile. These events are routinely managed in usual clinical practice and in a medical condition where close monitoring of patients is standard. Lilly therefore considers that hypersensitivity be removed from the safety specification as an important identified risk.

Oedema leading to congestive heart failure when insulin human is used concomitantly with thiazolidinediones, classified as an important identified risk in the previous RMP, is removed from the list of safety concerns.

Justification of Removal:

The Committee for Medicinal Products for Human Use had previously requested Lilly to include 'oedema leading to CHF when insulin human is used concomitantly with TZD's as an important identified risk for insulin human. It was subsequently added to the label, including the Core Data Sheet, and to the Initial RMP as an important identified risk, as the request to include it as a risk was made under the prevailing GVP Module V (Rev 1) guidelines, in place at the time. This request appeared to be consistent with the guidance in the Rev 1 guideline, which indicated that 'impact on the individual patient' was a consideration in determining which risks were considered important.

In September 2010, the European Medicines Agency recommended the suspension of marketing authorisation for rosiglitazone-containing antidiabetes medicines in Europe (EMA 2010), following the publication of studies which found an increased cardiovascular risk of rosiglitazone (Graham et al. 2010; Nissen and Wolski 2010). While rosiglitazone-containing antidiabetic medications are now withdrawn from use in the European Union, pioglitazone-marketing authorisation remains active; however, the use of TZDs has dropped dramatically since this risk was identified. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) clinical practice guidelines for the Management of Hyperglycaemia in Type 2 Diabetes lists pioglitazone as an add-on in refractory patients only and warn that any potential reduction in HbA1c is at the expense of weight gain, fluid retention, and increased risk of heart failure (Inzucchi et al. 2015).

At the time of the initial RMP (Version 1), data lock through 30 June 2013, events of oedema leading to CHF due to concomitant use of insulins and TZD were considered very rarely reported (0.00008%) based on an estimated patient exposure to insulin human of more than 60.6 million patients. As of 30 June 2018, only 2 cases have been reported in Lilly safety system since 2013. Based on 70 events over 78.5 million patient-years of exposure cumulatively through 30 June 2018, the reporting rate for oedema leading to CHF when insulin human is used concomitantly with TZDs is considered very rare at 0.00009%.

The increased risk of oedema leading to CHF when insulins (both insulin lispro and insulin human) are used in combination with TZDs is adequately addressed as a warning in all insulin labels, is common knowledge among healthcare providers (HCPs), and occurs very rarely. Healthcare professionals are aware of the risk of oedema leading to CHF and have instituted appropriate measures within clinical practice, which has significantly decreased the number of AEs reported. Therefore, based on the clarifications presented in Rev 2 of GVP Module 5 and the current understanding of the ADR, it is no longer necessary to consider this well-characterised very rare ADR as an important identified risk requiring specific pharmacovigilance monitoring in the RMP. The insulin human label will continue to list the use

of the TZD (pioglitazone) in combination with insulin human under special warnings and precautions for use.

Medication Errors, classified as an important potential risk in the previous RMP, is removed from the list of safety concerns.

Justification of Removal:

All medicines are prone to medication errors; however the complexity of insulin therapy (different types of insulin used in the same patient, determination of correct dose, handling of syringes/pens, etc.) makes medication errors more likely. Due to the narrow therapeutic margin of insulin therapy, a medication error may have severe consequences such as severe hypoglycaemia. 'Medication error' is not a risk, as there are multiple events that may be coded to this term, involving dispensing, prescribing, administration, alleged device problem or other contributing factors which do not fulfil the criteria for risk or an important risk. According to GVP Module 5 (Rev 2) published in March 2017, it is the medically severe outcome that is considered a risk, which if frequent and supported by scientific evidence is then considered an important (identified or potential) risk. The important identified risk of a medication error is 'severe hypoglycaemia' and is already included in the safety specification as an 'important identified risk'; therefore, inclusion of medication errors as a separate important (potential) risk is not consistent with the RMP Rev 2 guidance and would be a potentially confusing addition, as several terms are coded as 'medication errors' which would never be associated with medically severe conditions or outcomes.

Antigenicity, classified as an important potential risk in the previous RMP, is removed from the list of safety concerns.

Justification of Removal:

Antigenicity is a laboratory abnormality and not a risk. According to GVP Module 5 (Rev 2) published in March 2017, it is the medically severe outcome that is considered a risk, which if frequent and supported by scientific evidence is then considered an important (identified or potential) risk.

Antigenicity is a term that describes the ability of a foreign protein to evoke the generation of antibodies. Frequently, these antibodies do not target the active ingredient, but rather pharmaceutical excipients (such as protamine). Long-term treatment with insulin human, similar to all other insulins, elicits a low and clinically inconsequential immunogenic response. As with other insulins, treatment with insulin human is associated with greater antibody responses in patients with T1DM than in those with T2DM.

Intermittent treatment does not exaggerate specific or cross-reactive antibody response. Patients treated with insulin human do not develop increased insulin dosage requirements nor do they experience an increase in events related to insulin allergy (Fineberg et al. 2003; Mianowska et al. 2011). The presence of antibodies against an insulin usually has no adverse clinical consequences. No AE of clinical relevance has been observed in many immunogenicity studies of insulin human (Fineberg et al. 1982, 1983; Mianowska et al. 2011).

Furthermore, events of antigenicity have not been associated with clinically significant outcomes. Lilly therefore considers that antigenicity be removed from the safety specification as an important potential risk.

Neoplasms, classified as an important potential risk in the previous RMP, is removed from the list of safety concerns.

Justification of Removal:

The risk of neoplasms with insulin use originally rose from Lantus (insulin glargine) data. Lantus is a long-acting recombinant human insulin analogue and differs from human insulin by 1 amino acid. Lantus contains glycine instead of asparagine in position A21 on the A-chain and includes the addition of 2 arginine molecules on positions B31 and B32, leading to a higher affinity of insulin glargine for the insulin-like growth factor 1 (IGF-1) receptor compared to human insulin (Heinemann et al. 2000; Mannucci 2012). Historically, the potential risk of neoplasms with Lantus was based on its enhanced affinity for IGF-1 receptors and increased mortality observed in 1 trial, which raised concern for both cardiovascular safety and malignancy risk (Colhoun and SDRN Epidemiology Group 2009; Currie et al. 2009; Hemkens et al. 2009; Jonasson et al. 2009; Smith and Gale 2009).

As Lantus binds most tightly to IGF-1 receptor compared to any other analogues such as insulin human or insulin lispro, in theory, it would have the highest risk for proliferation. However, the results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial – an international, multicentre, randomised, controlled clinical trial with exposure to Lantus for a medium duration of 6.2 years – showed no increase in the risk of any cancer (HR 1.00 [95% CI: 0.88-1.13; p=0.97]) or death from cancer (HR 0.94 [95% CI: 0.77-1.15; p=0.52]) and a neutral effect on cardiovascular outcome (ORIGIN Trial Investigators 2012). Thus, the proposal to remove the risk is primarily supported by both scientific evidence, including literature, and understanding of mechanistic plausibility. Combination products such as insulin degludec/insulin aspart do not list neoplasms as a risk, further supporting that in both long-acting (insulin degludec) and short-acting (insulin aspart) insulins, neoplasms is not considered an important identified or potential risk.

While published literature has noted that the background rate of certain neoplasms is higher in patients with diabetes compared to the general population (Giovannucci et al. 2010; Shikata et al. 2013), there currently is no clinical or in vivo evidence to indicate that any commercially available insulin analogue has carcinogenic effects (Tennagels and Werner 2013).

Both DM and cancer are chronic diseases that are increasing in prevalence and share common risk factors. Epidemiological studies showed that diabetes, particularly type 2, is associated with some types of cancer with variable strengths, for example, strongly associated with liver, pancreas, and endometrial cancers; moderately associated with colorectal, breast, and bladder cancers; and not associated with lung cancer (Vigneri et al. 2009). In addition, epidemiological studies suggest comorbidity with diabetes may increase mortality in patients with cancer (Barone et al. 2008). Although biological plausibility for the association of hyperglycaemia and hyperinsulinemia with cancer has been described (Giovannucci et al. 2010), the association

remains inconclusive. It is unclear if the association is causal in nature, indirectly associated by a common risk factor, or diabetes itself is a manifestation of underlying metabolic derangement that causes or promotes neoplastic processes. No relationship between duration of treatment and the occurrence of neoplasms has been established for insulin human.

A recent consensus statement of the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) (Handelsman et al. 2013) confirmed the many unknowns about the association between diabetes, obesity, the various treatment options, and the risk to develop cancer, which was specified as a concern only if insulins were used at very high doses.

Based on the estimated cumulative worldwide insulin human exposure over 78.5 million patient-years (through 30 June 2018), neoplasms have been reported at an incidence of 0.002%, which is considered to be very rarely reported. Furthermore, neoplasms have been closely monitored during routine surveillance activities for many years, and no signal has been identified since its inclusion in the initial EU-RMP.

The findings in Lilly postmarketing database are consistent with neoplasms in the diabetic patient population. The most commonly reported cancers in the diabetic population are liver, pancreas, endometrium, kidney, breast, prostate, bladder, and colorectal cancer (Ballotari et al. 2017). Men and women are generally equally affected. Over half (53%) of all cancers are diagnosed in adults aged 50 to 74 years (Cancer Research UK 2018). In the age group above 65 years, there are many confounders due to lifestyle choices as well as multiple comorbidities requiring polypharmacy. In treatment of T2DM, most patients attempt to achieve glycaemic control by utilising oral diabetes medications from the 7 available classes (biguanides, sulphonylureas, alpha-glucosidase inhibitors, TZDs, meglitinides, dipeptyl peptidase-4 inhibitors, and sodium-glucose lowering transport inhibitors), prior to using insulin. These patients are also often treated with medications for hypertension, hyperlipidaemia, as well as therapies to prevent vascular complications of diabetes. These factors make it difficult to attribute neoplasms to a specific medication.

If not managed appropriately, diabetes is a life-threatening condition. The available evidence supports treatment as the benefit outweighs the risk of neoplasm. The consensus statement of AACE/ACE (Handelsman et al. 2013) provides an extensive analysis on the interaction between diabetes, obesity, antihyperglycaemic treatment, and malignancies. The authors conclude that when discussing diabetic treatment overall, the contribution to cancer development appears to be relatively small or nonexistent. Additionally, review of the labels and risks of more recently approved insulin products (for example, FiAsp, Ryzodeg, Levemir, and Apidra) reveals that most do not consider neoplasms as an important potential risk.

No safety-related signal for neoplasm has been detected with insulin human since its inclusion in the initial EU-RMP. The spontaneous postmarketing reporting rate is considered very rarely reported, and the published literature does not provide any compelling evidence of a causal relationship between the insulin human treatment and an increased risk of carcinogenicity.

Taking into account all the scientific data presented above, Lilly does not consider neoplasms an important potential risk for insulin human.

Hypoglycaemia, classified as an important identified risk in the previous RMP, is changed to **'Severe hypoglycaemia'** in the list of safety concerns, and remains an important identified risk.

Justification of change:

The majority of hypoglycaemic episodes are easily detectable by patients and can be treated with oral glucose. Severe hypoglycaemia is considered an important identified risk because it can lead to severe medical consequences including coma, seizures, and very rarely death (see Section SVII.3.1 for details).

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: Severe hypoglycaemia

Potential mechanisms:

Serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability, and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake, energy expenditure, or both. Insulin is included on the Institute for Safe Medication Practices List of High-Alert Medications. Medications appearing on this list represent increased risk of causing significant harm if used in error. The most severe potential consequence of insulin associated medication errors is severe hypoglycaemia; however, all medicines are prone to medication errors. In the case of insulin use, including insulin human, potential reasons for medication errors associated can be categorised into 1 of 5 sources: prescribing, dispensing, administration, alleged device problem, or other. The complexity of insulin therapy (different types of insulin used in the same patient, determination of correct dose, handling of syringes/pens, etc.) makes medication errors more likely. Due to the narrow therapeutic margin of insulin therapy, a medication error may have severe consequences. The most severe consequence of medication errors is severe hypoglycaemia, which is considered an important identified risk for insulin human.

Evidence source(s) and strength of evidence:

As described in the Summary of Product Characteristics (SmPC), hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes experience. The majority of hypoglycaemic episodes are easily detectable by patients and can be treated with oral glucose; however, severe hypoglycaemia is an event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions

(Seaquist et al. 2013). Severe hypoglycaemia is considered an important identified risk because it can lead to severe medical consequences including coma, seizures, and very rarely death (Inzucchi et al. 2012).

In postmarketing data, there have been 10,432 hypoglycaemic events in 9600 cases (77.5% nonserious and 22.5% serious) reported cumulative through 30 June 2018. In 78.5 million patient-years of exposure, 62 events had a fatal outcome (0.00008%), 2600 events were considered recovered (0.003%), 27 recovered with sequelae (0.00003%), 508 recovering (0.0006%), 630 not recovered (0.0008%), 3 worsened (0.000004%), 6 disability/incapacitated (0.000008%), and in 6596, the outcome was unknown (0.008%). Based on an estimated exposure to insulin human of 78.5 million patient-years of exposure, events of hypoglycaemia are considered rarely reported (0.01%), and severe hypoglycaemia (important identified risk) is very rare (<0.01%).

Characterisation of the risk:

The incidence of severe hypoglycaemia in clinical trials is highly variable and is affected by study design, insulin formulations, concomitant medications, and definition of severe hypoglycaemia.

In the literature, rates of severe hypoglycaemia vary between 62 and 170 episodes per 100 patient-years in T1DM and 3 and 73 episodes per 100 patient-years in T2DM (Cryer et al. 2003). About 2% to 4% of deaths among patients with T1DM are attributable to severe hypoglycaemia (Briscoe and Davis 2006).

Risk factors and risk groups:

Risk factors affecting glucose homeostasis include age, tight glycaemic control, hypoglycaemic unawareness, and years of insulin therapy. Risk groups include very young children and the elderly population as severe hypoglycaemia is most common at the extremes of age (Frier et al. 2014). Studies in T1DM reported the incidence of severe hypoglycaemia to be almost 2-fold in patients aged >60 years (4.01 episodes per person per year) compared to patients aged <60 years (2.43 episodes per person per year) (Schütt et al. 2012). Strict glycaemic control has also been associated with an increased risk of severe hypoglycaemia in patients with both T1DM and T2DM, especially when BG is not measured frequently. Patients with an impaired awareness of hypoglycaemia is also associated with an increased incidence of severe hypoglycaemia and is more common in T1DM (20% to 25%) than in insulin-treated T2DM (<10%) (Frier et al. 2014). Persons with decreased cognitive ability may be predisposed to an increased risk of severe hypoglycaemia, as suggested in one study in patients with T2DM (Punthakee et al. 2012). While the duration of the disease is a major risk factor for hypoglycaemia, the risk of severe hypoglycaemia increases with complications of the disease, such as progressive renal impairment (Frier et al. 2014).

Preventability:

Severe hypoglycaemia is unpredictable, as insulin requirements for each patient frequently change and are determined by a multitude of factors. Patient education is important in preventing severe hypoglycaemia. Desired behaviours include regular eating habits, frequent measuring of BG, and general adherence to treatment. Most patients learn how to recognise the symptoms of hypoglycaemia and are able to take preventative measures, such as oral carbohydrate ingestion, and modifying food intake with respect to physical activity, before it becomes severe.

Additionally, human error in patient or HCP use can be reduced but not eliminated. Making information resources available to patients and HCPs on an ongoing basis plays an important part in the prevention of severe hypoglycaemia resulting from medication errors. Furthermore, employing different colours on labels and contrasting fonts on packages may help the user distinguish 1 insulin from another. The literature describes successful measures, such as the development of a second person check system and avoidance of abbreviations when writing the prescription ("High-alert' medications and patient safety [Patient safety alert]" 2001).

Impact on the risk-benefit balance of the product:

As described in the Summary of Product Characteristics (SmPC), hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. The majority of hypoglycaemic episodes can be treated with oral glucose. However, severe hypoglycaemia can lead to coma, seizure, or death. In the literature, rates of severe hypoglycaemia vary between 62 and 170 episodes per 100 patient-years in T1DM and 3 and 73 episodes per 100 patient-years in T2DM (Cryer et al. 2003). It is expected that severe hypoglycaemia would continue to be readily managed in usual clinical practice and therefore the impact on risk-benefit balance will remain low.

Public health impact:

Hypoglycaemia is the main risk for all commercially available insulins. Selvin et al. (2016) estimated, using NHANES data, that the proportion of patients with diabetes currently on any insulin treatment (includes insulin only and insulin plus oral diabetes medications) has been relatively stable since 1988 (29.1% of patients in 2005-2012, 24.8% in 1999-2004, and 30.3% in 1988-1994). Hypoglycaemia may be defined in different ways, and the severity of hypoglycaemic symptoms may differ between patients. For patients with T1DM and advanced T2DM, insulin therapy is necessarily and frequently life-saving; therefore, the benefits outweigh the risks. In the light of this requirement, the impact on public health is considered to be low.

SVII.3.2 Presentation of the Missing Information

Missing Information:

Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect (LODE), or hypoglycaemia with the new manufacturing process ([redacted])

Anticipated risk/consequence of the missing information:

The Medicines and Healthcare products Regulatory Agency (MHRA) raised concerns about the potential increase in the risks of hypersensitivity and antigenicity due to the transition of patients to insulin human manufactured by a different process ([redacted]).

[redacted]

Taking into account the scientific evidence, Lilly considers the likelihood of any untoward events related to the change in manufacturing to be low. For a limited time, additional pharmacovigilance activities have been put in place to monitor changes in the reporting of AEs related to hypersensitivity, antigenicity, and lack of drug effect (LODE).

[redacted]

[redacted]

[redacted] The current analyses confirm the lack of evidence for any changes in the safety profile.

Following the forthcoming analysis, the influence of the changes to the manufacturing process is unlikely to be regarded as having potential influence on the incidence of hypersensitivity,

immunogenicity, local injection site reactions, LODE, or hypoglycaemia. However, additional analyses of these changes are ongoing, and this will remain as 'Missing Information' in Table SVIII.1 until analyses are completed. If at that time, there is no cause for safety concern, then it will be removed from the RMP. Additional information on the manufacturing change and protamine sourcing can be found in Part III.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Severe Hypoglycaemia
Important potential risks	None
Missing information	Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect (LODE), or hypoglycaemia with the new manufacturing process [redacted]

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for severe hypoglycaemia:

A follow-up form is used routinely to obtain structured information on spontaneously reported suspected adverse reactions of special interest for low blood sugar. These forms were in place prior to the creation of the initial RMP, and continue to be used to obtain details regarding hypoglycaemia, including information on the severity of the event.

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.

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 human insulin manufacturing changes [redacted] This evaluation includes a side-by-side comparison of cases from finished drug product batches using final insulin product batches product using drug substance from [redacted], compares that data set with control data from cases reported using both chimeric historic and chimeric concurrent process drug substance, and analyses and reports the results of the assessments. This commitment is outlined in Part III.2 and Part III.3.

III.2 Additional Pharmacovigilance Activities

Pharmacovigilance activities related to Manufacturing Changes: [redacted]

[redacted] The analyses shall also be included in the annual periodic safety update reports (PSUR) submitted to the FDA and the PSUR submitted to the EU every 3 years.

In addition, after appropriate signal analysis and clarification, any monthly assessment that identifies a possible DEC that might indicate an event related to the manufacturing change shall be forwarded to the authority within 15 days of completion.

[redacted]

Rationale and objective:

These additional pharmacovigilance activities are in place to address potential changes in the frequency of hypersensitivity, immunogenicity, local injection site reactions, or LODE or hypoglycaemia (increased drug effect) events.

The objective is to determine any potential increase in the frequency of these specific AEs reported in patients receiving insulin human manufactured according to the new process when compared to the frequency observed with the previous manufacturing process.

Study design:

This study is a post-authorisation retrospective pharmacovigilance analysis of AE reports.

Batches of Interest

Adverse event reports submitted for product batches including insulin human produced from the [redacted] as it is introduced for patient use are compared to reports submitted for batches including insulin human produced from the old process. Insulin human products of interest include Humulin S, Humulin I, and Humulin M3. Batch numbers will be used to distinguish products produced from each process.

Events of Interest

Designated events of interest that may denote [redacted] of insulin human will include LODE, increased drug effect and hypoglycaemia, and hypersensitivity, local injection site reactions, and immunogenicity. Specific AEs within these designated categories of events will be defined by the preferred term hierarchy of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the report.

Milestones:

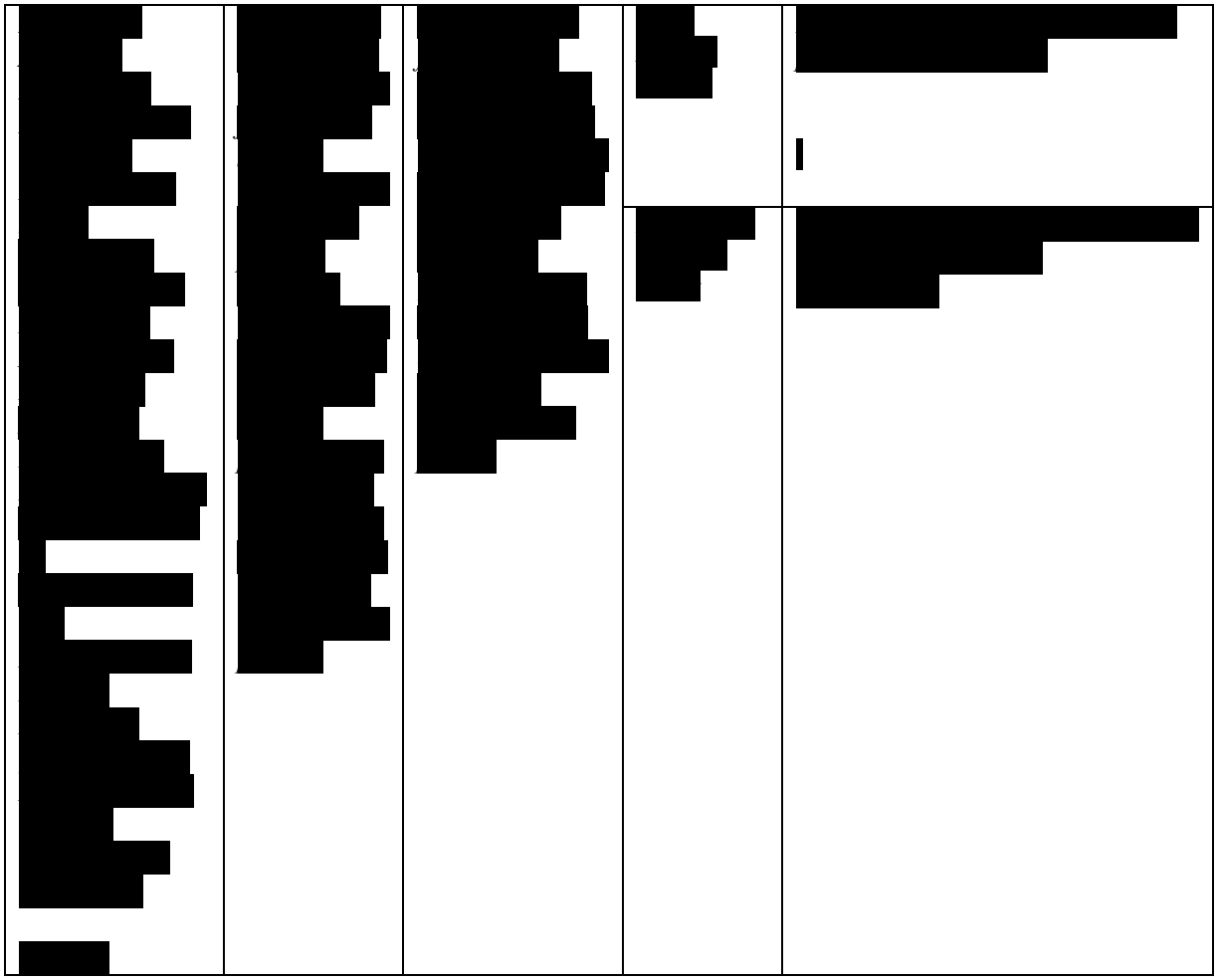
Milestone	Planned date
Start of data collection	[redacted]
Study Progress Reports[b]	[redacted]
End of data collection	[redacted]
Final report of study results	[redacted]

[redacted]

III.3 Summary Table of Additional Pharmacovigilance Activities

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

Study (study short name, and title) **Status** (planned/ongoing)	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due date**
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation (key to benefit risk)				
None.				
Category 2 – Imposed mandatory additional PV activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None.				
Category 3 – Required additional pharmacovigilance activities (by the competent authority)				



Abbreviations: PV = pharmacovigilance; rDNA = recombinant DNA.

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

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Severe Hypoglycaemia	Routine risk communication: • SmPC Section 4.3 (contraindications) • SmPC Section 4.4 (special warnings and precautions for use) • SmPC Section 4.7 (effects on ability to drive and use machines) • SmPC Section 4.8 (undesirable effects) • SmPC Section 4.9 (overdose) • PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 (special warnings and precautions for use) recommends that transferring patients to another type or brand of insulin should be done under strict medical supervision. • SmPC Section 4.9 (overdose) provides information on the management of mild hypoglycaemic episodes, moderately severe hypoglycaemia, and severe hypoglycaemia resulting in coma. • PL Sections 2 and 4 describe causes and warning signs of mild, moderate, and severe low blood sugar, how to avoid hypoglycaemia, recommend testing blood glucose often, and provide information on how to deal with mild, moderate, and severe hypoglycaemia. Product differentiation to address the risk: • Unique packaging and labelling of insulin human products is intended to facilitate the differentiation between different insulin human preparations and also between insulin human and the insulins of other manufacturers for patient and healthcare providers. • For the Humulin U-100 KwikPen formulations and prefilled injection devices, Colour Coded Dose Knobs have been established in the EU to help patients in identifying the correct type of insulin. Other routine risk minimisation measures beyond the Product Information: • Pack size: not applicable • Legal status: not applicable
Missing information: Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect	Routine risk communication: • Not applicable Routine risk minimization activities recommending specific clinical measure to address the risk: • Not applicable Other routine risk minimisation measures beyond the Product Information:

(LODE), or hypoglycaemia with the new manufacturing process [redacted]	• Pack size: not applicable • Legal status: not applicable

Abbreviations: EU = European Union; [redacted]; PL = package leaflet; SmPC = Summary of Product Characteristics.

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

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe Hypoglycaemia	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • SmPC Section 4.9 • PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 (special warnings and precautions for use) recommends that transferring patients to another type or brand of insulin should be done under strict medical supervision. • SmPC Section 4.9 (overdose) provides information on the management of mild hypoglycaemic episodes, moderately severe hypoglycaemia, and severe hypoglycaemia resulting in coma. • PL Sections 2 and 4 describe causes and warning signs of mild, moderate, and severe low blood sugar, how to avoid hypoglycaemia, recommend testing blood glucose often, and provide information on how to deal with mild, moderate, and severe hypoglycaemia. Product differentiation to address the risk: • Unique packaging and labelling of insulin human products is intended to facilitate the differentiation between different insulin human preparations and also between insulin human and the insulins of other manufacturers for patient and healthcare providers. • For the Humulin U-100 KwikPen formulations and prefilled injection devices, Colour Coded Dose Knobs have been established in the EU to help patients in identifying the correct type of insulin. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Spontaneous case AE follow-up form for hypoglycaemia • Monthly AE/PC Surveillance Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information: Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect (LODE), or hypoglycaemia with the new manufacturing process ([redacted])	Routine risk minimization measures: • None or not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None or not applicable Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Monthly lot-specific AEs and comparative analysis [redacted] Additional pharmacovigilance activities: Post-approval safety surveillance programme for lot-specific AE review and analysis (surveillance, Category 3) • Cumulative analysis submitted semi-annually to the authority within 30 days of completion; • Summary of analysis also included in the PSUR

Abbreviations: AE = adverse event; EU = European Union; [redacted] PC = product complaint; PL = package leaflet; PSUR = periodic safety update report; SmPC = Summary of Product Characteristics.

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 risks	Severe Hypoglycaemia
Important potential risks	None
Missing information	Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect (LODE), or hypoglycaemia with the new manufacturing process [redacted]

Abbreviation: [redacted]

II.B Summary of Important Risks

Important identified/potential risk: Severe Hypoglycaemia

Important identified/potential risk: Severe Hypoglycaemia	
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • SmPC Section 4.9 • PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 (special warnings and precautions for use) recommends that transferring patients to another type or brand of insulin should be done under strict medical supervision. • SmPC Section 4.9 (overdose) provides information on the management of mild hypoglycaemic episodes, moderately severe hypoglycaemia, and severe hypoglycaemia resulting in coma. • PL Sections 2 and 4 describe causes and warning signs of mild, moderate, and severe low blood sugar, how to avoid hypoglycaemia, recommend testing blood glucose often, and provide information on how to deal with mild, moderate, and severe hypoglycaemia. Product differentiation to address the risk: • Unique packaging and labelling of insulin human products is intended to facilitate the differentiation between different insulin human preparations and also between insulin human and the insulins of other manufacturers for patient and healthcare providers. • For the Humulin U-100 KwikPen formulations and prefilled injection devices, Colour Coded Dose Knobs have been established in the EU to help patients in identifying the correct type of insulin. Additional risk minimization measures: • None

Abbreviations: EU = European Union; package leaflet; SmPC = Summary of Product Characteristics.

Important Missing Information: Potential change in the incidence of hypersensitivity, immunogenicity, local injection site reactions, lack of drug effect (LODE), or hypoglycaemia with the new manufacturing process [redacted]	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-approval safety surveillance programme for lot-specific adverse event review and analysis (surveillance, Category 3) • Cumulative analysis submitted semi-annually to the authority within 30 days of completion; • Summary of analysis also included in the PSUR See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: PSUR = periodic safety update report.

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

Pharmacovigilance activities related to Manufacturing Changes: [redacted]

[redacted]

Rationale and objective:

These additional pharmacovigilance activities are in place to address potential changes in the frequency of hypersensitivity, immunogenicity, local injection site reactions, or LODE or hypoglycaemia (increased drug effect) events.

The objective is to determine any potential increase in the frequency of these specific AEs reported in patients receiving insulin human manufactured according to the new process when compared to the frequency observed with the previous manufacturing process.

There are no studies required for Humulin.

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

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
[redacted]	[redacted]	[redacted]	MR-BHI [redacted]

Table 2. Annex II: Completed Studies

None.

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	[redacted]

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

Approved protocols:

[redacted]

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific adverse event follow-up form	Event(s) associated with the form
Low Blood Sugar – Complex	Hypoglycaemia
Low Blood Sugar – Simple	Hypoglycaemia

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)

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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	See Cover Page	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.

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