

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

ENTUZITY™ KwikPen®

(insulin injection, human biosynthetic)

Solution for Injection, 500 units/mL

THERAPEUTIC CLASSIFICATION

Anti-Diabetic Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION..... 3

SUMMARY PRODUCT INFORMATION 3

DESCRIPTION..... 3

INDICATIONS AND CLINICAL USE..... 3

CONTRAINDICATIONS 4

WARNINGS AND PRECAUTIONS..... 4

ADVERSE REACTIONS..... 11

DOSAGE AND ADMINISTRATION 16

OVERDOSAGE 19

ACTION AND CLINICAL PHARMACOLOGY 19

STORAGE AND STABILITY..... 21

DOSAGE FORMS, COMPOSITION AND PACKAGING 21

PART II: SCIENTIFIC INFORMATION 23

PHARMACEUTICAL INFORMATION..... 23

CLINICAL TRIALS..... 24

DETAILED PHARMACOLOGY 25

TOXICOLOGY 26

REFERENCES 29

PART III: PATIENT MEDICATION INFORMATION 30

ENTUZITY™ KwikPen®
(insulin injection, human biosynthetic)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Solution for injection 500 units/mL in 3mL disposable prefilled pen, (1,500 units of insulin)	Glycerin, metacresol, zinc oxide, water for injection. Sodium hydroxide and hydrochloric acid are used during manufacture to adjust the pH.

DESCRIPTION

ENTUZITY™ (insulin injection, human biosynthetic) is a concentrated human insulin formulation. ENTUZITY is produced by recombinant DNA technology in a non-disease-producing special laboratory strain of *E. coli* that has been genetically altered by the addition of the human gene for insulin production. ENTUZITY is an aqueous, sterile, clear and colourless solution of biosynthetic human insulin.

INDICATIONS AND CLINICAL USE

- ENTUZITY is a concentrated human insulin indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day.
- The safety and efficacy of ENTUZITY used in combination with other insulins has not been determined.
- The safety and efficacy of ENTUZITY delivered by continuous subcutaneous infusion has not been determined.
- ENTUZITY should not be used for the treatment of emergencies such as diabetic coma and pre-coma and patients with diabetes undergoing surgeries.

Pediatrics (<18 years of age):

No studies of ENTUZITY have been conducted in the pediatric population (see WARNINGS AND PRECAUTIONS, Special Populations).

Geriatrics (>65 years of age)

There is limited evidence available in geriatric patients aged 65 to ≤ 75 . Patients > 75 years of age have not been studied (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

ENTUZITY is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- During episodes of hypoglycemia (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin, including ENTUZITY. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes (see WARNINGS AND PRECAUTIONS, Hypoglycemia).
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death (see WARNINGS AND PRECAUTIONS, Hypoglycemia).
- ENTUZITY should not be transferred from the prefilled pen to other devices, such as a syringe. The markings on the insulin syringe will not measure the dose correctly (see WARNINGS AND PRECAUTIONS, Medication Errors Prevention, DOSAGE and ADMINISTRATION). Overdose can result causing severe hypoglycemia.
- To minimize the risk of hypoglycemia do not administer ENTUZITY intravenously, intramuscularly or in an insulin pump. Do not dilute or mix ENTUZITY with any other insulin products or solutions (see DOSAGE AND ADMINISTRATION).
- Any change including changes in insulin, manufacturer, type, concentration, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased (see WARNINGS AND PRECAUTIONS, Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen).
- Never use ENTUZITY if it has become viscous (thickened) or cloudy or if it has formed a deposit of solid particles on the wall of the cartridge; use it only if it is clear and colourless (see DOSAGE AND ADMINISTRATION).
- Medication errors have been reported for concentrated insulins. To avoid medication errors, always verify the product label before each injection (see WARNINGS AND PRECAUTIONS, Medication Errors Prevention, DOSAGE AND ADMINISTRATION).

General

ENTUZITY is a five-times concentrated version of a human insulin solution currently approved and marketed in Canada as HUMULIN R (100 units/mL). ENTUZITY and HUMULIN R have different time-action profiles and thus are not equivalent (see ACTION AND CLINICAL PHARMACOLOGY). Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in life-threatening hypoglycemia. Severe hypoglycemia may develop up to 24 hours after the original injection. As with all insulin therapies, the duration of action of ENTUZITY may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature, and level of physical activity.

The number and size of daily doses and the time of administration, as well as diet and exercise, are items that require direct and continuous medical supervision. Stress or concomitant illness, especially infectious and febrile conditions, or diseases of the adrenal, pituitary or thyroid glands, may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose (see Part III: PATIENT MEDICATION INFORMATION).

Hypokalemia

Hypokalemia is among the potential clinical adverse effects associated with the use of ENTUZITY and all other insulin therapies. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. This potential clinical adverse effect may be more relevant in patients who are at risk for hypokalemia [e.g. patients using potassium lowering drugs, patients taking medications sensitive to serum potassium concentrations, or patients losing potassium through other means (e.g., diarrhea)] (see OVERDOSAGE). Monitor potassium levels in patients at risk for hypokalemia.

Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, concentration or method/timing of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia, and may result in the need for a change in dosage. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetes treatment may be needed. If an adjustment is needed, it may be done with the first doses or during the first few weeks or months and under medical supervision (see DOSAGE AND ADMINISTRATION, Switching to ENTUZITY).

When patients are transferred between types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may change or become less pronounced than those experienced with their previous insulin.

Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.

Insulin initiation and glucose control intensification

Patients whose blood glucose is greatly improved, e.g., by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycemia and should be advised accordingly. Intensification or rapid improvement in glucose control has been associated with a transitory

reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, acute painful peripheral neuropathy, and peripheral edema. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Never Share an ENTUZITY KwikPen Between Patients

To avoid transmission of disease, the ENTUZITY KwikPen should never be used by more than one person, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Insulin plus Thiazolidinediones (TZDs)

TZDs, alone or in combination with other antidiabetes agents (including insulin), can cause heart failure and edema. The combination of insulin, including ENTUZITY, with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD Product Monograph Warnings and Precautions information when the use of these drugs in combination with any insulin, including ENTUZITY, is contemplated.

Medication Errors Prevention

Medication errors have been reported for concentrated insulins, often due to errors in dispensing, prescribing, or administration. Attention to details at all levels may prevent these errors.

Prescribing Errors

- The ENTUZITY KwikPen is specifically designed for delivering this 500 units/mL concentrated insulin. NO dose conversion is required when prescribing the ENTUZITY KwikPen (see DOSAGE AND ADMINISTRATION, Dosing Considerations).
- The prescribed dose of ENTUZITY should always be expressed in units of insulin.

Dispensing Errors

- Patients and caregivers should be instructed to always inspect insulin KwikPens to confirm that the correct insulin is dispensed, including the correct insulin brand and concentration.
- The ENTUZITY KwikPen is aqua in colour and includes a distinct green rectangular box with white lettering indicating the concentration of 500 units/mL.
- The ENTUZITY KwikPen delivers insulin doses in 5-unit increments (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Administration Errors

- To avoid medication errors between ENTUZITY and other insulins, patients and caregivers should be instructed to always check the insulin label before each injection.
- Patients and caregivers should NOT perform dose conversion when using the ENTUZITY KwikPen. The dose window of the ENTUZITY KwikPen shows the number of units of ENTUZITY to be injected.
- Patients and caregivers must visually verify the units of the dose prior to administering ENTUZITY. The dose must not be selected by counting the number of audible clicks made by the KwikPen. A requirement for a patient to self-administer is that they can read

the dose scale. Patients who are blind or have poor vision must be instructed to always get assistance from another person who has good vision and is trained in the administration of insulins.

- Patients and caregivers should NOT transfer ENTUZITY from the ENTUZITY KwikPen into any syringe for administration as overdose and severe hypoglycemia can occur [see WARNINGS AND PRECAUTIONS].
- The ENTUZITY KwikPen is for single patient use only [see WARNINGS AND PRECAUTIONS].
- Patients must also be instructed to not re-use needles. A new sterile needle must be attached before each injection. Re-use of needles increases the risk of blocked needles which may cause underdosing or overdosing.
- In the event of a future hospitalization or visit to the Emergency Department, patients should inform hospital or Emergency Department staff of the dose of ENTUZITY prescribed.

Carcinogenesis and Mutagenesis

Human insulin is produced by recombinant technology. No serious events have been reported in subchronic toxicology studies. Human insulin was not mutagenic in a battery of in vitro and in vivo genetic toxicity assays (see TOXICOLOGY).

Endocrine and Metabolism

Hypoglycemia

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapies, including ENTUZITY. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death (see ADVERSE REACTIONS). Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in life-threatening hypoglycemia. Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Severe hypoglycemia may develop up to 24 hours after the original injection of insulin human injection (500 U/mL).

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see OVERDOSAGE).

Hypoglycemia can occur regardless of the type of insulin taken and may cause fatigue, sweating, heart palpitations, disturbed behavior, hunger, convulsions, or loss of consciousness. In extreme circumstances, even death can occur without recognizable symptoms.

In certain cases (e.g., long duration of diabetes mellitus, diabetic nerve disease, intensified diabetes mellitus control, transferring patients from other insulin, patients who experience recurrent hypoglycemia, patients with psychiatric illness, elderly patients or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycemia (pallor, sweating, anxiety, headache, tachycardia, hunger) may change or be less pronounced.

Concomitant disease in the kidney, liver or affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.

Changes in insulin therapy, changes to co-administered medication, or changes in lifestyle (i.e., diet, exercise/physical activity) may require a change in dosage to avoid hypoglycemia. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation (see ACTION AND CLINICAL PHARMACOLOGY). As with all insulin preparations, the glucose lowering effect time course of ENTUZITY may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Glucose monitoring is recommended for all patients with diabetes mellitus who are taking ENTUZITY or other insulin products. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood monitoring is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery) especially in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. Patients with diabetes should be instructed to carry a few lumps of sugar or glucose tablets, or candies or biscuits to prevent the progression of a hypoglycemic reaction, should one occur (see Part III: PATIENT MEDICATION INFORMATION).

Hyperglycemia

Inadequate dosing or discontinuation of ENTUZITY, especially in type 1 diabetes mellitus, may lead to hyperglycemia and when untreated, hyperglycemic events may eventually lead to diabetic ketoacidosis or coma, which are potentially fatal (see ADVERSE REACTIONS). Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include polydipsia, polyuria, nausea, abdominal pain, vomiting, drowsiness, blurred vision, flushed dry skin, loss of appetite, weight loss, as well as acetone odor of breath (see ADVERSE REACTIONS).

Ability to concentrate and react may be impaired as a result of hyperglycemia or as a result of hyperglycemia-induced visual impairment. This may constitute a risk in situations where these abilities are of special importance such as when driving a car or operating machinery.

Hepatic/Biliary/Pancreatic

The effect of hepatic impairment on the pharmacokinetics of ENTUZITY has not been studied. Insulin requirements may be decreased in the presence of hepatic impairment. In patients with

hepatic impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis.

Immune

Local Allergic Reactions

Patients taking ENTUZITY may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass (see ADVERSE REACTIONS). These reactions may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients (see CONTRAINDICATIONS). Localized reactions and generalized myalgia have been reported with injected metacresol, which is an excipient of ENTUZITY.

Rarely, subcutaneous administration of insulin products, including ENTUZITY can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) which may affect insulin absorption. Patients should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions.

Systemic Allergic Reactions

Systemic allergic reactions have rarely occurred with insulin treatments, including ENTUZITY (see ADVERSE REACTIONS). These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema, and drop in blood pressure (see ADVERSE REACTIONS).

Severe cases of generalized allergy including anaphylactic reaction may be life-threatening. If hypersensitivity reactions occur, discontinue ENTUZITY; treat per standard of care and monitor until symptoms and signs resolve (see CONTRAINDICATIONS).

Antibody Production

Immune responses can occur with insulin products, including production of auto antibodies (IgG). The presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hypoglycemia or hyperglycemia. In general, glycemic control is not affected by the presence of auto antibodies. Insulin antibodies are frequently cross-reactive. Patients who have demonstrated an allergic reaction to other insulin products may demonstrate an allergic reaction to ENTUZITY.

Renal

The effect of renal impairment on the pharmacokinetics of ENTUZITY has not been studied. The requirements for insulin may be reduced in patients with renal impairment. In patients with renal impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis.

Reproduction Studies

There are no adequate and well-controlled studies with ENTUZITY during pregnancy and lactation.

Information for Patients

Patients should be informed about potential advantages and disadvantages of ENTUZITY therapy, including possible side effects. Patients should also be offered continued education and advice on insulin therapies, delivery device options, lifestyle management, self-monitoring, complications of insulin therapy, timing of dosage, and instruction for use of injection devices, storage of insulin, travelling and others (see PART III: PATIENT MEDICATION INFORMATION).

Special Populations

Pregnant Women

ENTUZITY has not been studied in pregnancy. ENTUZITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. . Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

Patients with diabetes should be advised to inform their doctor 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. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Reproduction and fertility studies were not performed in animals.

Nursing Women

Because many drugs, including human insulin, are excreted into human milk, caution should be exercised when ENTUZITY is administered to a nursing woman. Women with diabetes who are lactating may require adjustments in their insulin dose.

Pediatrics (<18 years of age)

No studies of ENTUZITY have been conducted in the pediatric population. Standard precautions as applied to use of ENTUZITY in adults are appropriate for use in children. As in adults, the dosage of ENTUZITY in pediatric patients must be individualized based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatrics (≥65 years of age)

The effect of age on the pharmacokinetics and pharmacodynamics of ENTUZITY has not been studied. In a 24 week study, 65/323 (20%) ENTUZITY-treated patients with type 2 diabetes were ≥ 65 and ≤ 75 years of age. There were no overall differences in the safety or effectiveness between these and younger subjects in the study. Geriatric patients > 75 years of age have not

been studied (see CLINICAL TRIALS).

Caution should be exercised when ENTUZITY is administered to geriatric patients. Hypoglycemia may be difficult to recognize in the elderly. In general, dose selection for an elderly patient should take into consideration the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.

Other Disease States

The presence of diseases such as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma can complicate the control of diabetes mellitus.

Monitoring and Laboratory Tests

With insulin therapy, including ENTUZITY, regular blood glucose self-monitoring is recommended to obtain optimal glycemic control (see PART III: PATIENT MEDICATION INFORMATION). Increase monitoring frequency including periodic overnight readings with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity, in patients with renal or hepatic impairment, in geriatric patients, in patients with hypoglycemia unawareness, and in patients co-administered medications known to affect glucose metabolism or mask the symptoms of hypoglycemia (see WARNINGS AND PRECAUTIONS, Hypoglycemia and DRUG INTERACTIONS). Periodic measurement of hemoglobin A1c is recommended for the monitoring of long-term glycemic control.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of ENTUZITY has not been evaluated in a placebo-controlled or active comparator-controlled study. The data in Table 1 reflect the exposure of 323 ENTUZITY-treated patients in an open-label Phase 4 clinical trial of adult patients (18 to \leq 75 years of age) with type 2 diabetes mellitus requiring >200 units of insulin per day who had not achieved glycemic control on U-100 insulins (>200 to \leq 600 units/day) with or without oral antidiabetic drugs (OADs). A total of 325 patients were randomly assigned to take ENTUZITY either three times daily (TID) or twice daily (BID) before meals for 24 weeks. Of these patients, 323 received at least 1 dose of ENTUZITY. The mean duration of exposure was 22 weeks in both the TID and BID treatment groups.

The incidence of discontinuation due to adverse events was 2.5% for both dosing groups (8 patients discontinued in total; 4 patients from each dosing group). Two of the 8 patients (0.6%)

discontinued due to acute myocardial infarction. No other event terms leading to discontinuation were reported by more than a single patient.

A total of 55/323 (17%) patients (TID, 28 [17.3%] and BID, 27 [16.8%]) experienced ≥ 1 serious adverse event (SAE). The most frequently reported SAEs were:

- severe hypoglycemia (TID, 3 patients [1.9%] and BID, 6 patients [3.7%]),
- acute myocardial infarction (TID, 3 patients [1.9%] and BID, 1 patient [0.6%]),
- cardiac failure congestive (TID, 1 patient [0.6%] and BID, 3 patients [1.9%]),
- pneumonia (TID, 1 patient [0.6%] and BID, 3 patients [1.9%]), and
- chest pain (TID, 2 patients [1.2%] and BID, 2 patients [1.2%]).

Overall, 10/162 (6.2%) TID patients and 18/161 (11.2%) BID patients reported treatment-emergent adverse events (TEAEs) possibly related to study drug; those reported by more than a single patient were:

- hypoglycemia (TID, 3 patients [1.9%] and BID, 6 patients [3.7%]),
- abnormal weight gain (TID, 3 patients [1.9%] and BID, 2 patients [1.2%]),
- oedema peripheral (TID, 1 patient [0.6%] and BID, 3 patients [1.9%]), and
- weight increased (TID, 1 patient [0.6%] and BID, 2 patients [1.2%]).

Table 1 provides a listing of the TEAEs reported with a frequency of $\geq 1\%$ of ENTUZITY-treated patients.

Table 1: Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of ENTUZITY-treated Patients with Type 2 Diabetes up to 24 Weeks

Adverse Event	ENTUZITY TID (N=162) n (%)	ENTUZITY BID (N=161) n (%)	ENTUZITY Total (N=323) n (%)
Cardiovascular			
Cardiac failure congestive	3 (1.9)	4 (2.5)	7 (2.2)
Acute myocardial infarction	3 (1.9)	1 (0.6)	4 (1.2)
Coronary artery disease	2 (1.2)	2 (1.2)	4 (1.2)
Ear and Labyrinth Disorders			
Ear pain	2 (1.2)	2 (1.2)	4 (1.2)
Gastrointestinal Disorders			
Diarrhoea	6 (3.7)	10 (6.2)	16 (5.0)
Vomiting	4 (2.5)	11 (6.8)	15 (4.6)
Nausea	4 (2.5)	9 (5.6)	13 (4.0)
Abdominal discomfort	5 (3.1)	5 (3.1)	10 (3.1)
Abdominal pain	2 (1.2)	5 (3.1)	7 (2.2)
Constipation	4 (2.5)	1 (0.6)	5 (1.5)
Gastroesophageal reflux disease	1 (0.6)	4 (2.5)	5 (1.5)
Abdominal distension	3 (1.9)	1 (0.6)	4 (1.2)
General Disorders and Administration Site Conditions			
Oedema peripheral	7 (4.3)	10 (6.2)	17 (5.3)
Oedema	5 (3.1)	4 (2.5)	9 (2.8)
Pyrexia	2 (1.2)	7 (4.3)	9 (2.8)
Fatigue	3 (1.9)	5 (3.1)	8 (2.5)
Chest pain	4 (2.5)	3 (1.9)	7 (2.2)

Peripheral swelling	4 (2.5)	3 (1.9)	7 (2.2)
Pain	3 (1.9)	4 (2.5)	7 (2.2)
Influenza like illness	2 (1.2)	2 (1.2)	4 (1.2)
Infections and Infestations			
Viral upper respiratory tract infection	14 (8.6)	20 (12.4)	34 (10.5)
Upper respiratory tract infection	13 (8.0)	9 (5.6)	22 (6.8)
Bronchitis	9 (5.6)	5 (3.1)	14 (4.3)
Influenza	7 (4.3)	7 (4.3)	14 (4.3)
Gastroenteritis viral	5 (3.1)	8 (5.0)	13 (4.0)
Sinusitis	7 (4.3)	6 (3.7)	13 (4.0)
Ear infection	4 (2.5)	5 (3.1)	9 (2.8)
Pneumonia	3 (1.9)	6 (3.7)	9 (2.8)
Urinary tract infection	4 (2.5)	4 (2.5)	8 (2.5)
Cellulitis	2 (1.2)	5 (3.1)	7 (2.2)
Fungal infection	1 (0.6)	3 (1.9)	4 (1.2)
Tooth infection	3 (1.9)	1 (0.6)	4 (1.2)
Injury, Poisoning and Procedural Complications			
Ligament sprain	4 (2.5)	1 (0.6)	5 (1.5)
Muscle strain	2 (1.2)	3 (1.9)	5 (1.5)
Fall	4 (2.5)	0	4 (1.2)
Investigations			
Weight increased	6 (3.7)	5 (3.1)	11 (3.4)
Alanine aminotransferase increased	1 (0.6)	5 (3.1)	6 (1.9)
Aspartate aminotransferase increased	1 (0.6)	3 (1.9)	4 (1.2)
Metabolism and Nutrition Disorders			
Hypoglycaemia	3 (1.9)	6 (3.7)	9 (2.8)
Abnormal weight gain	3 (1.9)	2 (1.2)	5 (1.5)
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	3 (1.9)	10 (6.2)	13 (4.0)
Back pain	7 (4.3)	5 (3.1)	12 (3.7)
Arthralgia	7 (4.3)	1 (0.6)	8 (2.5)
Musculoskeletal pain	1 (0.6)	5 (3.1)	6 (1.9)
Muscle spasms	1 (0.6)	4 (2.5)	5 (1.5)
Trigger finger	2 (1.2)	3 (1.9)	5 (1.5)
Myalgia	2 (1.2)	2 (1.2)	4 (1.2)
Nervous System Disorders			
Headache	13 (8.0)	6 (3.7)	19 (5.9)
Hypoaesthesia	5 (3.1)	3 (1.9)	8 (2.5)
Migraine	2 (1.2)	3 (1.9)	5 (1.5)
Paraesthesia	1 (0.6)	4 (2.5)	5 (1.5)
Dizziness	1 (0.6)	3 (1.9)	4 (1.2)
Psychiatric Disorders			
Insomnia	3 (1.9)	2 (1.2)	5 (1.5)
Renal and Urinary Disorders			
Nephrolithiasis	3 (1.9)	1 (0.6)	4 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders			
Dyspnoea	9 (5.6)	9 (5.6)	18 (5.6)
Oropharyngeal pain	4 (2.5)	7 (4.3)	11 (3.4)
Asthma	2 (1.2)	6 (3.7)	8 (2.5)
Cough	3 (1.9)	5 (3.1)	8 (2.5)
Dyspnoea exertional	6 (3.7)	1 (0.6)	7 (2.2)

Nasal congestion	2 (1.2)	4 (2.5)	6 (1.9)
Chronic obstructive pulmonary disease	1 (0.6)	4 (2.5)	5 (1.5)
Respiratory tract congestion	0	4 (2.5)	4 (1.2)
Sinus congestion	2 (1.2)	2 (1.2)	4 (1.2)
Sleep apnoea syndrome	1 (0.6)	3 (1.9)	4 (1.2)
Skin and Subcutaneous Tissue Disorders			
Rash	5 (3.1)	4 (2.5)	9 (2.8)
Vascular Disorders			
Hypertension	3 (1.9)	3 (1.9)	6 (1.9)

Abbreviations: BID = twice daily; TID = three times daily.

Based on Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including ENTUZITY (see WARNINGS AND PRECAUTIONS, Hypoglycemia).

In the phase 4, open-label, trial described above, severe hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. In total, 9 out of 323 patients with type 2 diabetes reported 1 event each of severe hypoglycemia (TID, 3 patients [1.9%] and BID, 6 patients [3.7%]), including 1 event with a fatal outcome in a patient randomized to the BID treatment group.

The incidence of documented symptomatic hypoglycemia (signs or symptoms of hypoglycemia with glucose \leq 3.9 mmol/L) was 91.0% (294/323) overall. The event rate per patient-year in the TID group was 41.50 events per patient-year and in the BID group 51.55 events per patient-year.

The incidence of nocturnal documented symptomatic hypoglycemia (any documented symptomatic hypoglycemic event that occurred between bedtime and waking) was 79.3% (256/323). The event rate per patient-year in the TID group was 11.08 events per patient-year and in the BID group 14.40 events per patient-year.

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, rash, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including ENTUZITY and may be life-threatening (see WARNINGS AND PRECAUTIONS, Immune).

Lipodystrophy

Long-term use of insulin, including ENTUZITY, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect insulin absorption. Rotate insulin injection site within the same region to reduce the risk of lipodystrophy (see WARNINGS AND PRECAUTIONS, Immune and DOSAGE AND ADMINISTRATION).

Injection Site Reactions

Patients taking ENTUZITY may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and

injection site mass (see WARNINGS AND PRECAUTIONS, Immune).

Weight Gain

Weight gain has occurred with insulin therapy, including ENTUZITY, and has been attributed to the anabolic effects of insulin. In the clinical program, after 24 weeks of treatment, T1D patients gained an average of 5.4 kg and BID patients gained an average of 4.9 kg (see CLINICAL TRIALS).

Peripheral Edema

Insulin, including ENTUZITY, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy (See WARNINGS AND PRECAUTIONS, Insulin initiation and glucose control intensification).

Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The presence of antibodies that affect clinical efficacy may necessitate dosage adjustments to correct for tendencies toward hyper- or hypoglycemia (see WARNINGS AND PRECAUTIONS, Immune).

The incidence of antibody formation with ENTUZITY is unknown.

Less Common Clinical Trial Adverse Drug Reactions (<1% possibly related as reported by investigator)

The following adverse drug reactions possibly related to ENTUZITY were reported in <1% of ENTUZITY-treated patients:

Cardiac disorders: cardiac failure congestive.

Gastrointestinal disorders: abdominal distension.

General disorders and administration site conditions: oedema.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood cholesterol increased, blood triglycerides increased, gamma-glutamyltransferase increased, low density lipoprotein increased, weight increased.

Metabolism and nutrition disorders: fluid retention.

Neoplasms benign, malignant and unspecified (including cysts and polyps): prostate cancer.

Nervous system disorders: brain injury, headache, syncope, tremor.

Product issues: needle issue

Respiratory, thoracic, and mediastinal disorders: dyspnoea.

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drug-Drug Interactions

A number of medicinal products are known to interact with the glucose metabolism. Therefore, an increased frequency of glucose monitoring may be required when ENTUZITY is co-administered with these drugs.

The following substances may reduce insulin requirement:

Antidiabetic agents (e.g. GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors), ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), anabolic steroids, and sulfonamide antibiotics.

The following substances may increase insulin requirement:

Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, corticotropin, danazol, diphenylhydantoin, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.

The following substances may reduce or increase insulin requirement:

Octreotide/lanreotide, alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The following substances may mask the symptoms of hypoglycemia:

Beta-blockers, clonidine, guanethidine, and reserpine.

Insulin plus Thiazolidinediones (TZDs)

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia (see WARNINGS AND PRECAUTIONS and OVERDOSAGE).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ENTUZITY is reserved for the treatment of patients with diabetes requiring total daily doses of more than 200 units of insulin (basal and/or bolus).

Each ENTUZITY KwikPen contains 1,500 units of insulin and can deliver from 5 to 300 units per injection. The prefilled pen has been specifically designed for ENTUZITY; the pen delivers doses in 5-unit increments, and the dose window shows the number of units to be injected. ENTUZITY should not be transferred from the prefilled pen to other devices, such as a syringe. The markings on an insulin syringe will not measure the dose correctly. Overdose can result causing severe hypoglycemia.

The insulin solution from the ENTUZITY KwikPen should not be used in an insulin infusion pump.

Patients should carefully follow the prescriber's instructions for starting different concentration insulins or switching from standard to different concentration insulins. Close blood glucose monitoring is recommended during the transition and in the initial weeks thereafter.

ENTUZITY is a clear, colourless solution. It is important to always examine the appearance of the cartridge in the prefilled pen. It should not be used if it has become viscous (thickened) or cloudy or if it has formed a deposit of solid particles on the wall of the cartridge.

The ENTUZITY KwikPen is for single-patient use only. To prevent the possible transmission of disease, never share the ENTUZITY KwikPen between patients, even if the needle is changed.

Patients and caregivers must also be instructed to not re-use needles. A new sterile needle must be attached before each injection. Re-use of needles increases the risk of blocked needles which may cause under-dosing or over-dosing.

Patients and caregivers must visually verify the units of the dose prior to administering ENTUZITY. The dose must not be selected by counting the number of audible clicks made by the KwikPen. A requirement for a patient to self-administer is that they can read the dose scale. Patients, who are blind or have poor vision, must be instructed to always get assistance from another person who has good vision and is trained in administration of insulins.

Recommended Dose and Dosage Adjustment

ENTUZITY should be given two or three times daily. The dosage, number of injections, and timing of ENTUZITY should be determined by the physician, according to the requirement of the patient. ENTUZITY should be administered 30 minutes before a meal.

Recommended proportions for doses

If the patient follows a twice daily regimen: it is recommended that the total daily dose of ENTUZITY is divided into the initial proportions of 60% and 40% for administration 30 minutes before morning and evening meals, respectively.

If the patient follows a three times daily regimen: it is recommended that the total daily dose of ENTUZITY is divided into the initial proportions of 40%, 30% and 30% for administration 30 minutes before morning, midday and evening meals, respectively.

Dose adjustment may be required, for example, if the patient's timing of administration, weight or lifestyle changes or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see WARNINGS AND PRECAUTIONS). The dose may also have to be adjusted during concurrent illness (see WARNINGS AND PRECAUTIONS). Any change in insulin dose should be made under medical supervision.

Switching to ENTUZITY

HUMULIN R and ENTUZITY have different time-action profiles and are not equivalent. These insulins are not directly interchangeable (see ACTION AND CLINICAL PHARMACOLOGY).

Switching from basal/bolus or mixed insulins with lower concentration to ENTUZITY can be done on a unit-to-unit basis for the total daily dose of insulins (basal plus bolus). No dose conversion is required when transferring a patient from a different insulin concentration; however, dose adjustment may be needed to achieve target ranges for plasma glucose levels.

- If the patient's HbA1c at the time of switching is $\leq 8\%$, it is recommended that the total daily dose of ENTUZITY is reduced by 20% on a unit-to-unit basis.
- If the patient's HbA1c at the time of switching is $> 8\%$, it is recommended that the total daily dose is continued on a unit-to-unit basis.

Close blood glucose monitoring is recommended after switching and in the initial weeks thereafter.

Administration

ENTUZITY should only be given by subcutaneous injection. ENTUZITY should not be administered intravenously or intramuscularly. ENTUZITY should not be mixed with other insulins and should not be diluted.

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 ENTUZITY to ensure that a blood vessel has not been entered. After any insulin injection, the injection site should not be massaged. Patients must be educated to use proper injection techniques.

Each pack contains a patient information leaflet with information on how to inject insulin and an instructions for use leaflet for the ENTUZITY KwikPen.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia (see WARNINGS AND PRECAUTIONS). Hypoglycemia may occur in any patient receiving insulin and is most commonly manifested by hunger, nervousness, warmth and sweating, and palpitations. Other symptoms may include headache, confusion, drowsiness, fatigue, anxiety, blurred vision, diplopia, or numbness of the lips, nose, or fingers. The clinical manifestations of hypoglycemia can be masked by the concomitant administration of certain substances (see DRUG INTERACTIONS).

Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

Hypokalemia must be corrected appropriately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Regulation of glucose metabolism is the primary activity of insulins, including ENTUZITY. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

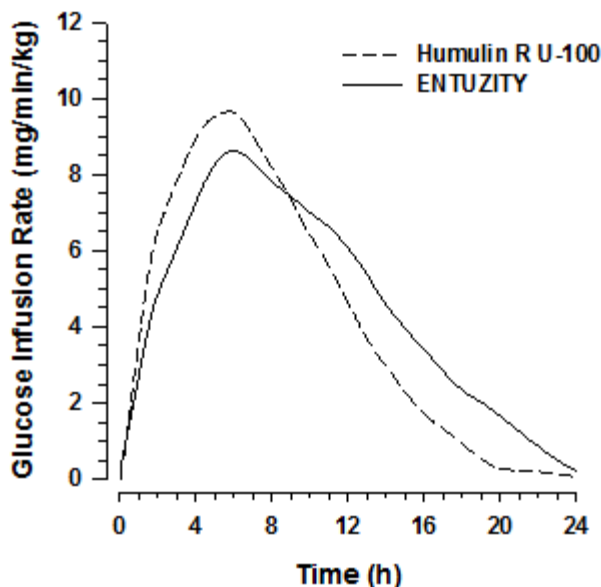
Pharmacodynamics

The pharmacodynamics of ENTUZITY compared to HUMULIN R were evaluated in a euglycemic clamp study of 24 healthy obese subjects (BMI = 30-39 kg/m²). Following single subcutaneous doses of 50 units (0.4 - 0.6 units/kg) (data not shown) and 100 units (0.8-1.3 units/kg) (Figure 1), the mean time of onset of action of ENTUZITY was 14 minutes for the 50 U dose and 13 minutes for the 100 U dose (range 3-58 minutes). For HUMULIN R, the mean time of onset of action was 16 minutes for the 50 U dose and 11 min for the 100 U dose (range 4-44 minutes). At the 100 U dose, the maximum effect of ENTUZITY was lower and occurred later than that of HUMULIN R. The duration of action of 100 U dose of ENTUZITY (approximately 21 hours; range 17- 24 hours) was longer than that of 100 U dose of HUMULIN R. Thus, ENTUZITY exhibited time-action characteristics reflecting both prandial and basal activity.

No pharmacodynamics studies were conducted in patients with diabetes mellitus.

Figure 1 should be considered only as a representative example since the time course of action of insulin may vary in different individuals or within the same individual. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables.

Figure 1: Mean Insulin Activity Versus Time Profiles After Subcutaneous Injection of a 100 Unit Dose of ENTUZITY or HUMULIN R to Healthy Obese Subjects.



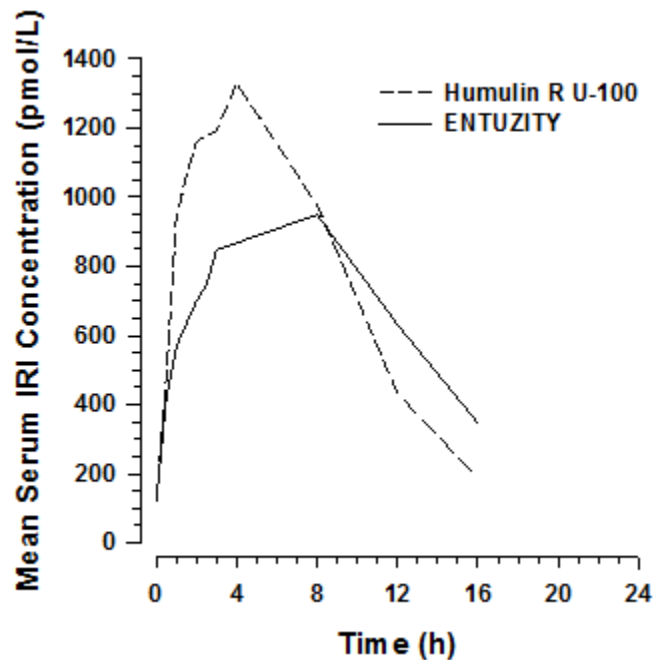
Pharmacokinetics

The pharmacokinetic profile of ENTUZITY compared to HUMULIN R was evaluated in a euglycemic clamp study of 24 healthy obese subjects (BMI range: 30-39 kg/m²). Following single subcutaneous doses of 50 units (data not shown) and 100 units (Figure 2), mean peak serum insulin concentrations were lower for ENTUZITY relative to HUMULIN R. The time to median peak insulin levels was 4.0 hours (range: 0.5-8.0 hours) for ENTUZITY 50 U dose and 8.0 hours (range: 0.5-8.0 hours) for 100 U dose. The time to median peak insulin levels was 3.0 hours (range: 1.0 - 8.0 hours) for both the HUMULIN R 50 U and 100 U doses.

In the same study, the mean apparent half-life of insulin was approximately 4.5 hours (range 1.9 -10 hours) for ENTUZITY and 3.6 hours (range 1.6 - 8.6 hours) for HUMULIN R.

No pharmacokinetic studies were performed in patients with diabetes mellitus.

Figure 2: Mean Serum Insulin Concentrations Versus Time After Subcutaneous Injection of a 100 Unit Dose of ENTUZITY or HUMULIN R to Healthy Obese Subjects.



STORAGE AND STABILITY

Protect from heat and light. Do not freeze. Do not use ENTUZITY after the expiration date printed on the label or if it has been frozen.

Not In-Use (Unopened) ENTUZITY KwikPen

Unopened containers should be stored refrigerated at 2°C to 8°C (36°F to 46°F) until time of use. Do not use if it has been frozen.

In-Use (Opened) ENTUZITY KwikPen

Do NOT store in-use pen devices refrigerated. Pen devices must be stored unrefrigerated at a maximum temperature of 30°C (86°F), and the pen must be discarded after 28 days, even if the pen still contains ENTUZITY. Once the container has been punctured, the chemical and physical stability for the drug product has been demonstrated for 28 days at a maximum temperature of 30°C (86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ENTUZITY (500 units per mL) is a clear and colourless aqueous solution available in:

- 3 mL KwikPen (prefilled pen, 1,500 units of insulin), packages of 2 or 5. (Not all pack sizes may be marketed.)

Non-medicinal ingredients include: glycerin, metacresol, zinc oxide, and water for injection. Hydrochloric acid and sodium hydroxide are used to adjust pH.

A4.0 LINR500-0000-CA-PM-YYYYMMDD

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

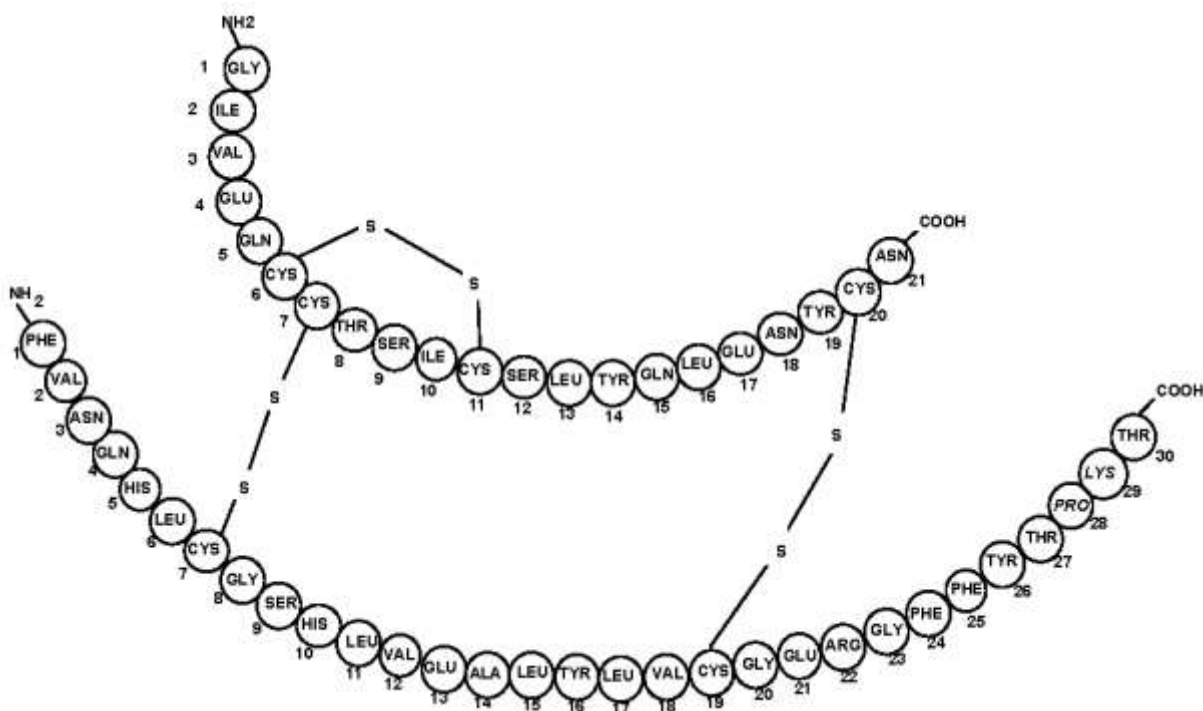
Proper name: ENTUZITY

Chemical name: Insulin injection, human biosynthetic

Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_6$

Molecular weight: 5807.72.

Structural formula:



Product Characteristics

ENTUZITY (insulin injection, human biosynthetic) is a polypeptide hormone consisting of a 21 amino acid A-chain and a 30 amino acid B-chain linked by two disulfide bonds. It is synthesized in a non-disease-producing special laboratory strain of *E. coli* that has been genetically altered by the addition of the human gene for insulin production.

CLINICAL TRIALS

Study IBHC: Comparing two dosing regimens of ENTUZITY in subjects with type 2 diabetes

The safety and efficacy of initiating, titrating, and maintaining two dosing regimens of ENTUZITY treatment was studied in an open-label, 24-week, parallel, 2-arm clinical trial of 323 subjects with type 2 diabetes. Before study entry, all subjects were taking high-dose (>200 to ≤600 units/day) U-100 insulin therapy (e.g. basal/bolus, premixed, basal only) with or without oral anti-diabetes drugs (OADs). Subjects underwent a 4-week lead-in period during which their daily U-100 insulin doses were verified and adjusted. U-100 was discontinued, and subjects were randomly assigned to one of two treatment arms: ENTUZITY three times per day (TID)(N=162) or ENTUZITY twice a day (BID)(N=161). ENTUZITY was given by subcutaneous injection 30 minutes before meals for a 12-week intensified dose-titration period followed by a 12-week maintenance dose-titration period. All OADs were continued except sulfonylureas and meglitinides. Daily doses of ENTUZITY were adjusted by study investigators during study visits using a titration-to-target algorithm to maintain subjects' self-monitored fasting/pre-meal, bedtime, or early morning blood glucose between 3.9 and 7.2 mmol/L.

The primary objective was to compare the change in hemoglobin A1c (HbA1c) from baseline to endpoint (24 weeks) between the TID and BID treatment regimens.

Subjects were 55.5 years of age (range 25-75 years) and had a mean duration since diabetes diagnosis of 15 years. 52.9% were male, 81.7% were Caucasian, and 19.2% were Hispanic. Mean body mass index (BMI) was 41.88 kg/m².

Mean HbA1c at baseline was 8.7% with 72% of subjects having HbA1c >8.0%. After 24 weeks, mean HbA1c was reduced in both ENTUZITY-treated groups compared to baseline (TID, -1.12% and BID, -1.22%). See Table 2 for a summary of other relevant results.

Table 2: Summary of Efficacy Results for ENTUZITY-Treated Subjects in Study IBHC

	Study IBHC (T2DM) 24-Week Endpoint	
	ENTUZITY TID	ENTUZITY BID
Subjects received ≥1 dose (n)	162	161
HbA1c (%) (Mean)		
Baseline HbA1c	8.72	8.73
Change from baseline, adjusted mean ^a	-1.12	-1.22
Percentage of subjects with HbA1c <7.0%	29	31
Fasting plasma glucose (mmol/L) (Mean)		
Baseline fasting plasma glucose	9.6	9.8
Change from baseline, adjusted mean ^b	-0.40	-0.35
Body weight (kg) (Mean)		
Baseline body weight	120.9	123.1
Change from baseline, adjusted mean ^a	5.44	4.87
Insulin Total Daily Dose (TDD) (units) (Mean)		
Baseline U-100 dose (at randomization)	287.1	287.3
Change from baseline U-100 dose to endpoint	55.3	51.2

ENTUZITY dose, adjusted mean ^a		
Number of injections (Median, [Range])		
Baseline injections	5 [2, 9]	5 [2, 10]
Change from baseline	-2 [-6, 1]	-3 [-8, 0]

Abbreviations: BID = twice daily; HbA1c = hemoglobin A1c; T2DM = type 2 diabetes mellitus; TDD = total daily dose; TID = three times daily.

^a Least squares mean from mixed-model repeated measures, with treatment and baseline alcohol consumption status as fixed effect.

^b Least square mean from analysis of covariance model (last observation carried forward method), with treatment and baseline alcohol consumption status as fixed effect.

DETAILED PHARMACOLOGY

The following sections are based on results of assessments using biosynthetic human insulin, 100 units/mL formulations.

Preclinical Pharmacology

Biosynthetic human insulin (BHI) has been studied extensively. In nearly all the studies, BHI was compared with native pancreatic human insulin as well as with purified pork insulin. The resulting data clearly indicate that BHI is chemically, physically, biologically and immunologically equivalent to the appropriate pancreatic insulin standards. BHI is prepared by the proinsulin route, starting with an *E. coli* fermentation using recombinant DNA-containing plasmids. The amino acid sequences of the insulin chains were found to be correct and the disulfide bonds were shown to be in the proper configuration. Additional chemical and physical studies verified that the normal structure of the human insulin molecule was integrally formed by the proinsulin process.

Further confirmation that BHI is structurally identical to pancreatic human insulin was provided by radioimmunochemical assays for insulin. BHI and pancreatic human insulin reacted identically in the insulin radioimmunoassay, a method that is sensitive to minor structural variations within the insulin molecule.

The biological activity of BHI was evaluated by a wide variety of *in vitro* techniques, all of which demonstrated that BHI and pancreatic human insulin are equivalent within experimental error. In addition, BHI was found to have a hypoglycemic potency equivalent to purified pancreatic insulins as determined by the USP rabbit assay.

BHI did not elicit an antigenic response when administered to *E. coli* polypeptide-sensitized rats and guinea pigs. In a clinical experiment, it was demonstrated that the anti-*E. coli* polypeptide antibody levels in 20 new patients with diabetes were the same regardless of whether the treatment was with BHI or purified pork insulin.

No antibodies specific to *E. coli* polypeptide have been detected in patient serum samples from over 1,350 patients.

Clinical Pharmacology

Clinical pharmacologic studies with biosynthetic human insulin (rDNA) demonstrate that generally the pharmacokinetics and pharmacodynamics of BHI and purified pork insulin (PPI) are the same. However, serum concentrations after BHI is administered subcutaneously may be higher or occur sooner than after PPI. These differences are generally ascribed to the greater solubility of BHI, which apparently is related to the presence of threonine instead of alanine on the B-30 position of the molecule.

Effects of BHI on substrates and other non-insulin and glucose parameters have been studied. Most investigators have reported that the suppression of endogenous insulin as indicated by serum C-peptide values was equivalent for BHI and PPI.

Growth hormone (GH) increase was also equivalent or slightly less with BHI. Prolactin response was less after BHI than with PPI, while the cortisol response to insulin hypoglycemia may be greater with BHI than with PPI. There was no difference in non-esterified fatty acid lowering or blood glycerol, lactate, or 3-hydroxybutyrate levels between BHI and PPI.

While the effects of BHI on suppression of human C-peptide usually are the same as those for PPI, BHI may affect other variables differently than PPI. Further studies would be needed to determine the significance of differences between BHI and PPI on prolactin, GH, and glucagon concentrations.

TOXICOLOGY

As with pork insulin, biosynthetic human insulin will be mainly used by subcutaneous injection in humans and, therefore, the majority of studies in animals have been performed using this route of administration. However, acute toxicity studies in monkeys and a subchronic study in dogs were performed using intravenous administration. The experiments for acute toxicity are presented in Table 4 and for subacute toxicity in Table 5 and are summarized as follows:

- The selection of dose levels of human insulin for the single and multiple dose studies in animals was restricted by the potent hypoglycemic activity of this compound. The pharmacological effects of insulin are well-known from many years of human therapy and therefore the toxicological studies were designed to evaluate adverse effects of possible impurities such as *E. coli* polypeptides.
- The minimal lethal subcutaneous dose of biosynthetic human insulin in rats and mice was greater than 10 units/kg. This dose was a large multiple of the initial human clinical trial dose and also much greater than the average daily therapeutic dose of insulin (0.6 units/kg/day).
- Dogs given a single subcutaneous dose of 2 units/kg or an intravenous dose of 0.1 unit/kg of human insulin evidenced hypoglycemia and related pharmacological effects but no significant toxicity.
- No compound-related toxic effects were observed when rats were given daily subcutaneous injections of 2.4 units/kg of biosynthetic human insulin for one month. Similarly, beagle dogs given daily subcutaneous injections of 2 units/kg or intravenous injections of 0.1 unit/kg of human insulin for one month evidenced marked hypoglycemia, but no adverse effects were seen on hematologic or serum chemistry

parameters and there were no pathologic changes. There was no evidence of tissue damage or irritation at the site of injection in the rats or dogs.

- Biosynthetic human insulin gave negative results in the Modified Ames, Rat Hepatocyte, and Chinese Hamster mutagenicity tests.

It can be concluded that injections of pharmacologically effective doses of biosynthetic human insulin in animals did not produce toxic effects. There were no findings that would preclude the use of this compound in humans.

Table 3: Acute Toxicity

Species	Number Per Dose	Route	Single Dose	Duration (Days)	Observations
Rats	10 females 10 males	SC	10 IU/kg	14	No mortality. Minimum lethal dose >10 IU/kg.
Mice	10 females 10 males	SC	10 IU/kg	14	No mortality. Alopecia in females on BHI. Minimum lethal dose >10 IU/kg.
Mice	10 females 10 males	SC	10 IU/kg	14	No mortality. Minimum lethal dose >10 IU/kg
Rats	10 females 10 males	SC	10 IU/kg	14	Significant tolerance of doses without signs of toxicity.
Dogs	2 females 2 males	SC	2 IU/kg	14	Significant tolerance of doses without signs of toxicity.
Monkeys	2 females 2 males	IV	1 IU/kg	14	Significant tolerance without signs of toxicity. Blood glucose values decreased sharply in all animals 15-20 minutes post administration.

Table 4: Subacute Toxicity

Species	Number Per	Route	Single Daily	Number of	Observations
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	Dose		Dose	Doses	
Rats	15 females 15 males	SC	2.4 IU/kg/day	30	No toxicologically important changes occurred.
Dogs	3 females 3 males	SC	2.0 IU/kg/day	30	One male on BHI experienced convulsions. Some ataxia and hypoactivity.
Dogs	4 females 4 males	IV	0.1 IU/kg /day	30	Decreased thrombocyte numbers. Minor changes in alanine transaminase activities.

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2. de la Peña A, Riddle M, Morrow LA, Jiang HH, Linnebjerg H, Scott A, Win KM, Hompesch M, Mace KF, Jacobson JG, Jackson JA. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects [published correction appears in *Diabetes Care.* 2014;37(8):2414]. *Diabetes Care.* 2011;34(12):2496-2501.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

ENTUZITY™ KwikPen® (insulin injection, human biosynthetic) Solution for Injection, 500 units/mL

www.lilly.ca

Lilly (*logo*)

Read this carefully before you start taking ENTUZITY (In-Too-Za-Tee) and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ENTUZITY.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common side effect of insulin, including ENTUZITY. As with all insulins, the timing of low blood sugar may be different depending on the type of insulin you take.
- All patients with diabetes should check their blood sugar.
- High or low blood sugar that is not corrected can cause loss of consciousness, coma, or death.
- Do not use a syringe to remove ENTUZITY from your ENTUZITY KwikPen. The markings on a syringe will not measure your dose correctly. A severe overdose can happen, causing low blood sugar, which may put your life in danger.
- To reduce the chance of low blood sugar, do not inject ENTUZITY into a vein or muscle. Do not use ENTUZITY in an insulin pump, dilute ENTUZITY, or mix it with any other type of insulin or solution.
- Any change in insulin dose, manufacturer, type, concentration, or how it is injected should be made carefully and only with your doctor's advice. Blood sugar should be checked more often when these types of changes are made.
- Only use ENTUZITY if it is clear and colourless.
- Errors have been reported with the use of concentrated insulins like ENTUZITY. Always check the label on your insulin before injecting your dose to be sure you have the correct medicine.

What is ENTUZITY used for?

- ENTUZITY is a synthetic human insulin that is used to control high blood sugar in patients with diabetes mellitus who need more than 200 units of insulin in a day.
- ENTUZITY contains 5 times as much insulin (500 units/mL) in 1 millilitre (mL) as synthetic human insulin (100 units/mL).
- It is not known if ENTUZITY is safe and effective in children or patients >75 years of age.
- ENTUZITY should not be used in combination with other insulins.
- ENTUZITY should not be used in an insulin pump.

How does ENTUZITY work?

Insulin is a hormone that decreases the amount of sugar in your blood and urine by increasing the uptake of sugar from your blood into various tissues, such as the liver, muscles, and fat.

When taken two times or three times per day as directed, ENTUZITY works as both a meal-time (short-acting) and basal (long-acting) insulin.

What are the ingredients in ENTUZITY?

Medicinal ingredients: insulin injection, human biosynthetic

Non-medicinal ingredients: Glycerin, metacresol, zinc oxide, water for injection. (Sodium hydroxide and hydrochloric acid may be added during manufacture to adjust the pH.)

ENTUZITY comes in the following dosage forms:

ENTUZITY is a clear and colourless aqueous biosynthetic insulin solution for injection (500 units/mL) and is available in a 3 mL ENTUZITY KwikPen (prefilled, 1,500 units of insulin).

Do not use ENTUZITY if:

- You are having an episode of low blood sugar (hypoglycemia).
- You have an allergy to human insulin or any of the ingredients in ENTUZITY or components of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENTUZITY. Talk about any health conditions or problems you may have, including if you:

- Have liver or kidney problems.
- Take other medicines, especially ones called TZDs (thiazolidinediones).
- Have heart failure or other heart problems. If you have heart failure, it may get worse if you take TZDs with ENTUZITY.
- Are pregnant, planning to become pregnant, or breast-feeding. It is not known if ENTUZITY will harm your unborn or breastfeeding baby.
- Have any endocrine disease such as: acromegaly (too much growth hormone), Cushing's syndrome (too much of the adrenal hormones or long-time use of cortisone-type drugs), hyperthyroidism (overactive thyroid gland), or pheochromocytoma (tumor of the adrenal gland).
- have low potassium or are taking potassium lowering medication.
- Have an illness, especially with nausea and vomiting, diarrhea and/or fever because this may cause your insulin needs to change.
- Have trouble with your adrenal, pituitary or thyroid glands, because your doctor may decide to change your insulin dose
- Change your exercise routine, usual diet, or if you travel.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

Before you start using ENTUZITY, talk to your healthcare provider about low blood sugar and how to manage it.

Other warnings you should know about:

- Do not share your ENTUZITY KwikPen with anyone, including family members, even if

the needle on the delivery device has been changed. You may pass on a serious infection or get a serious infection from the other person.

- Do not operate heavy machinery, until you know how ENTUZITY affects you.
- Do not drink alcohol or use over-the-counter medicines that contain alcohol.
- Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium-lowering drugs or losing potassium (e.g. diarrhea)
- Eye disorders: fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder
- Pain due to nerve damage: if your blood sugar level improves very fast, you may get nerve related pain; this is usually temporary
- Swelling around your joints: when you first start using ENTUZITY, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually temporary.

The following may interact with ENTUZITY:

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines can change your blood sugar level. This may mean your insulin dose has to change. So, before taking a medicine ask your doctor if it will affect your blood sugar and what action, if any, you need to take. You also need to be careful when you stop taking a medicine.

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)

- Other medicines for the treatment of diabetes
- Medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide
- Fibrates (medicine used for lowering high levels of blood fats)
- Monoamine oxidase inhibitors (MAOI) (medicines used to treat depression)
- Medicines used to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates
- Sulfonamide antibiotics (medicines used to treat infections)
- Somatostatin analogs, such as octreotide
- Fluoxetine
- Anabolic steroids

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)

- Atypical antipsychotics (e.g., olanzapine and clozapine)
- Hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), somatropin, thyroid hormones, glucagon.
- Corticosteroids (used to treat inflammation)
- Danazol (medicine acting on ovulation)
- Protease inhibitors (used to treat HIV infection)
- Diuretics (also called water pills), used to treat high blood pressure or fluid retention
- Isoniazid (used to treat tuberculosis)
- Some medicines used to treat asthma, such as albuterol, epinephrine, terbutaline

- Niacin and phenothiazines
- Corticotropin
- Diphenylhydantoin

If you take any of the medicines below, your blood sugar level may rise or fall

- High blood pressure medicines, such as: beta-blockers or clonidine
- Some medicines used to treat mental health problems, such as: lithium salts.
- Octreotide and lanreotide (used to treat a rare condition involving too much growth hormone (acromegaly))
- Alcohol (including wine and beer)
- A medicine used to treat some parasitic infections, called pentamidine. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Some medicines may make it harder to recognize the warning signs of your blood sugar being too low (hypoglycemia). Such medicines include: beta-blockers medicines, clonidine, guanethidine, or reserpine.

Do not use insulin together with medicines used to treat type 2 diabetes belonging to a class called Thiazolidinediones (TZDs). The use of these medicines together may increase your risk of developing heart failure.

How to take ENTUZITY:

- Use ENTUZITY exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much ENTUZITY to use and when to use it.
- Know the amount of ENTUZITY you use. Do not change the amount of ENTUZITY you use unless your healthcare provider tells you to.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.
- The ENTUZITY KwikPen is specially made to dial and deliver doses of ENTUZITY. Before injecting, select your dose based on the number of units shown in the dose window of the pen. Do not select your dose by counting the number of clicks. The pen is not recommended for use by the blind or visually impaired without the help of someone trained to use it.
- Do not use a syringe to remove ENTUZITY from your ENTUZITY KwikPen. The markings on a syringe will not measure your dose correctly. A severe overdose can happen, causing low blood sugar, which may put your life in danger.
- Use ENTUZITY two or three times a day 30 minutes before eating a meal. ENTUZITY is usually the only insulin that you will need.
- Inject ENTUZITY under your skin (subcutaneously). Do not use ENTUZITY in an insulin pump or inject ENTUZITY into your vein (intravenously) or your muscle (intramuscularly).
- Do not mix ENTUZITY in the KwikPen with any other type of insulin or liquid medicine.
- Change (rotate) your injection site with each dose.
- Check your blood sugar levels. Ask your healthcare provider what your blood sugar levels should be and when you should check your blood sugar levels.
- Keep ENTUZITY and all medicines out of reach of children.

- Your dose of ENTUZITY may need to change because of a change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take or stop taking.
- Do not reuse needles. Re-using needles increases the chances of blocking your needle, which may cause incorrect dosing.
- **NEEDLES AND PENS MUST NOT BE SHARED** with anyone including family members. Never share an ENTUZITY KwikPen, even if the needle on the delivery device is changed. You may pass on a serious infection or get a serious infection from the other person.

Overdose:

If you have injected too much ENTUZITY, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. If your blood sugar gets too low, immediately take action to increase your blood sugar level. See “Get emergency medical help if you have:” below for more information.

If you have injected too much ENTUZITY, your potassium may become too low (hypokalemia). Hypokalemia must be corrected by a healthcare professional.

If you think you have taken too much ENTUZITY, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed a dose of ENTUZITY or if you have not injected enough insulin, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, see Hyperglycemia section below.

Do not take a double dose to make up for a missed dose.

What are possible side effects from using ENTUZITY?

These are not all the possible side effects you may feel when taking ENTUZITY. If you experience any side effects not listed here, contact your healthcare professional. Please also see Serious Warnings and Precautions.

The following side effects may be observed while taking ENTUZITY:

- hypoglycemia (see Hypoglycemia section below).
- hyperglycemia (see Hyperglycemia section below).
- skin changes and reactions at the injection site (see Injection Site Reactions section below).
- allergic reactions (see Allergic Reactions section below).

Hypoglycemia (low blood sugar level)

Hypoglycemia is one of the most frequent adverse events experienced by insulin users.

Insulin reaction (too little sugar in the blood, also called "hypoglycemia") can be brought about

by:

- Taking too much insulin.
- Missing or delaying meals.
- Exercising or working too hard just before a meal.
- An infection or illness (especially with diarrhea or vomiting).
- A change in the body's need for insulin.
- A new insulin type, dose or schedule

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal due to nausea and vomiting, you should test your blood sugar level and notify your doctor.

The first symptoms of insulin reaction usually come on suddenly and may include vague symptoms of fatigue, nervousness or “shakiness”, rapid heartbeat, nausea, and a cold sweat. It is of utmost importance that you understand that these symptoms demand immediate attention. Severe hypoglycemia may happen up to 24 hours after your injection of ENTUZITY.

Your ability to concentrate and to react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery – see Serious Warnings and Precautions).

A few patients who experienced hypoglycemic reactions after being transferred to human insulin, such as ENTUZITY, have reported that these early warning symptoms were less pronounced than they were with animal-source insulin. Some people may not recognize when their blood sugar drops low (especially patients who have had diabetes for a long time, have diabetic nerve disease, whose blood sugar level improves quickly, who have switched from other insulin products, who experience recurring hypoglycemia, who have psychiatric illness, who are elderly, or who are using certain other medications).

Eating sugar or a sugar-sweetened product will often correct the condition and prevent more serious symptoms. Artificial sweeteners are not useful for the treatment of hypoglycemia.

If a person with diabetes becomes delirious or mentally confused, or suffers from loss of memory or delusions, diluted corn syrup or orange juice with sugar should be administered by mouth. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered. In the event of a hypoglycemic reaction, whether mild or severe, you should notify your doctor promptly so that any desirable change in diet or dosage can be determined.

Hyperglycemia

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- changes in your health (illness, stress, or emotional disturbances).
- not taking your insulin or taking less than recommended by your health care professional.
- malfunction and/or misuse of the KwikPen.
- eating significantly more than your meal plan suggests.
- a new insulin type, dose, or schedule.
- some new medications, including prescriptions, over-the counter medication, herbs, vitamins and street drugs.

Symptoms of hyperglycemia include:

- confusion or drowsiness.
- increased thirst.
- decreased appetite, nausea, or vomiting.
- rapid heart rate.
- increased urination and dehydration (too little fluid in your body).
- blurred vision.
- flushed dry skin.
- acetone (fruity) odor of breath.

Hyperglycemia can be mild or severe. **It can progress to high glucose levels, diabetic ketoacidosis (DKA), and result in unconsciousness and death.**

What to do if you experience hyperglycemia

- Test your blood sugar level and your urine for ketones as soon as you notice any of the above signs.
- Contact your doctor straight away if you have severe hyperglycemia or ketoacidosis.

Diabetic ketoacidosis (DKA)

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and ketones.

Symptoms of diabetic ketoacidosis include:

First symptoms:

- drowsiness.
- flushed face.
- thirst.
- loss of appetite.
- fruity smelling breath.
- rapid, deep breathing.
- abdominal (stomach area) pain.

Severe symptoms:

- heavy breathing.
- rapid pulse.

Prolonged hyperglycemia or diabetic ketoacidosis can lead to:

- nausea.

- vomiting.
- dehydration.
- loss of consciousness.
- death.

Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional. ENTUZITY should not be used to treat DKA, and people treating you should be advised that you are taking a concentrated long-acting insulin and about your regimen.

Allergic reactions

A patient may be allergic to an insulin product **including ENTUZITY**. Severe insulin allergies may be life-threatening. **If you have any of signs or symptoms of severe allergic reactions, seek medical help immediately.**

Signs of **severe** allergy include:

- a rash all over your body.
- shortness of breath.
- wheezing (trouble breathing).
- a fast pulse.
- sweating.
- low blood pressure.

Injection site reactions

Injecting insulin **including ENTUZITY** can cause the following reactions on the skin at the injection site:

- a little depression in the skin (lipoatrophy).
- skin thickening (lipohypertrophy).
- redness, pain, swelling, itching, hives, or inflammation at injection site.

You can reduce the chance of getting an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your health professional.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Heart Failure

Taking certain diabetes pills called thiazolidinediones or “TZDs” with ENTUZITY may cause or worsen heart failure in some people. This can happen even if you have never had heart failure or heart problems before.

Tell your healthcare provider if you have any new or worse symptoms of heart failure including:

- shortness of breath.
- swelling of your ankles or feet.
- sudden weight gain.

Get emergency medical help if you have:

- Severe hypoglycemia needing hospitalization or emergency room care, and be sure to tell the hospital staff the dose of ENTUZITY that your healthcare provider has prescribed for you.
- Trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

The most common side effects of ENTUZITY include:

- Low blood sugar (hypoglycemia), allergic reactions including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy), itching, and rash.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and/or get immediate medical help
	Only if severe	In all cases	
Severe Hypoglycemia Hypoglycemia symptoms: shakiness, sweating, impaired concentration, impaired reaction time.		✓	✓
Serious Hypersensitivity Reactions Hypersensitivity symptoms: itching in mouth, swelling of lips and/or tongue, shortness of breath, coughing, wheezing, and hives.		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
 - By calling 1-866-234-2345 (toll-free);
 - By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Address Locator 1908C
Ottawa, ON
K1A 0K9
- Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Protect from heat and light. Do not freeze. Do not use ENTUZITY after the expiration date printed on the label or if it has been frozen.

Not In-Use (Unopened) ENTUZITY KwikPen

Unopened containers should be stored refrigerated at 2°C to 8°C (36°F to 46°F) until time of use. Do not use if it has been frozen.

In-Use (Opened) ENTUZITY KwikPen

Do NOT store in-use pen devices refrigerated. Pen devices must be stored unrefrigerated at a maximum temperature of 30°C (86°F), and the pen must be discarded after 28 days, even if the pen still contains ENTUZITY. Once the container has been punctured, the chemical and physical stability for the drug product has been demonstrated for 28 days at a maximum temperature of 30°C (86°F).

Keep out of reach and sight of children.

If you want more information about ENTUZITY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.lilly.ca or by calling 1-888-545-5972.

ENTUZITY is a trademark owned by or licensed to Eli Lilly and Company, its subsidiaries or affiliates.

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly and Canada at: 1-888-545-5972 or visit the website at www.lilly.ca

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8

You may need to read this package insert again. Please do not throw away until you have finished your medicine.

Approved: MON-DD-YYYY

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