PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Schedule D

MYXREDLIN

INSULIN HUMAN IN 0.9% SODIUM CHLORIDE INJECTION

Sterile Solution for Intravenous Infusion, 1 Unit/mL

House Standard

Antidiabetic Agent

ATC Code: A10AB01

Baxter Corporation

7125 Mississauga Road

Mississauga, Ontario

L5N 0C2

Date of Initial Authorization:
August 3, 2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

Myxredlin (Insulin Human in 0.9% Sodium Chloride Injection) is a biosimilar biologic drug (biosimilar) to intravenously administered NOVOLIN® ge Toronto.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between MYXREDLIN and the reference biologic drug Novolin ge Toronto.

MYXREDLIN (Insulin Human in 0.9% Sodium Chloride Injection) is indicated for:

- The treatment of patients with diabetes mellitus who require insulin by intravenous administration for the control of hyperglycemia.

MYXREDLIN, using intravenous administration, should be used for the treatment of emergencies, such as diabetic coma and pre-coma, and in diabetics undergoing surgery. (See also *CONTRAINDICATIONS*)

1.1 Pediatrics

- Pediatrics (<18 years of age): No data are available to Health Canada.

1.2 Geriatrics

- Geriatrics (≥65 years): No data are available to Health Canada.

2 CONTRAINDICATIONS

Myxredlin is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- During episodes of hypoglycemia.
- In patients who are hypersensitive to human insulin or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulins products, the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins. (see HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (see ENDOCRINE AND METABOLISM – HYPOGLYCEMIA)
- Any transfer of insulin products should be made cautiously and only under medical supervision. (see WARNINGS AND PRECAUTIONS)
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision. (see WARNINGS AND PRECAUTIONS)
- This product shall not be used if it is not clear and colourless or if particulate matter or colouration is seen. (see DOSAGE AND ADMINISTRATION)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Concomitant stress or illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. In these instances, patients should contact their physicians and carefully control their blood glucose.

Inspect Myxredlin visually before use. It should appear clear and colourless. Do not use if particulate matter or colouration is seen.

Administer Myxredlin intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels (see WARNINGS AND PRECAUTIONS).

Do not add supplementary medication or additives.

Do not use in series connections.

Do not shake. Do not freeze. Discard any unused portion in accordance with local requirements.

4.2 Recommended Dose and Dosage Adjustment

The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty in the young or due to obesity) and lower in patients with residual, endogenous insulin production.

Dosage Adjustments

- Renal or hepatic impairment may reduce insulin requirement.
- Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet.
- In insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher.

4.4 Administration

Insulin solution should not be used if it does not appear water-clear and colourless.

Myxredlin is administered intravenously as an infusion. This should be carried out by healthcare professionals.

The infusion rate should be adjusted according to the individual circumstances and blood glucose levels. Monitoring of blood glucose is necessary during the insulin infusion.

5 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

Mild episodes of hypoglycemia can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes always carry some sugar candy.

Severe hypoglycemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse. Hypokalemia must be corrected appropriately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution for infusion, 100 units	Dibasic Sodium Phosphate Anhydrous, USP;

	insulin human in 100 mL 0.9% sodium chloride (1 unit per mL).	Monobasic Sodium Phosphate Monohydrate, USP; Sodium Chloride, USP; and Water for Injection, USP.

Myxredlin for intravenous use is a sterile, preservative-free, nonpyrogenic, clear, aqueous, and colourless solution supplied in a 100 mL GALAXY single-dose container. The pH range is 6.5 - 7.2.

Description

The active substance in Myxredlin is a polypeptide that is structurally identical to natural human insulin. Insulin human is produced by recombinant DNA technology in *Pichia pastoris*.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with all insulin products, the duration of Myxredlin may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including Insulin), can cause heart failure and oedema. The combination of Insulin 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 Myxredlin, is contemplated.

Carcinogenesis and Mutagenesis

See Part II – Scientific Information – NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia

As with other insulins, hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. Such reactions following treatment with Myxredlin are mostly mild and easily managed.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Myxredlin. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised

accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. (see ADVERSE REACTIONS and HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions, loss of consciousness, temporary or permanent impairment of brain function, or, in extreme circumstances, even death which can occur without recognizable symptoms.

Some people may not recognize when their blood sugar drops low.

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).

Patients should be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Glucose monitoring is recommended for all patients with diabetes.

Hepatic/Biliary/Pancreatic

There is no experience of the treatment with Myxredlin patients with hepatic impairment. As with other insulins, Myxredlin requirements may need to be adjusted in patients with hepatic impairment (see CLINICAL PHARMACOLOGY – Pharmacokinetics). As Myxredlin is used for treatment of diabetes mellitus, there is experience with treatment of pancreatic impairment concerned with diabetes mellitus, but not with other types pancreatic impairment.

Hyperglycemia

Inadequate dosing or discontinuation of insulin treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath (see ADVERSE REACTIONS). In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypokalemia

All insulin products, including Myxredlin, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for

hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, patients receiving intravenously administered insulin or patients losing potassium through other means (e.g., diarrhea)]. (see ADVERSE REACTIONS)

Immune

Local Allergic Reaction

As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Myxredlin.

Systemic Allergic Reaction

Systemic allergic reactions have rarely occurred with Myxredlin as with other insulin treatment. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening.

Antibody Production

Immune responses can occur in response to insulin. This may be associated with elevated IgG levels however this does not appear to affect HbA1c.

Human insulin is known to be antigenic, with low titres of antibodies developing in most patients (up to 80%). The effect of insulin antibodies on insulin pharmacokinetics, with the presence of binding IgG in serum, may delay time to peak levels of free insulin. Antibodies may be cross-reactive between different types of insulin.

Monitoring and Laboratory Tests

In patients with diabetes mellitus optimised metabolic control delays the onset and slows the progression of late diabetic complications. Optimised metabolic control, including glucose monitoring, is therefore recommended.

Renal

There is no experience of the treatment with Myxredlin patients with renal impairment. As with other insulins, Myxredlin requirements may need to be adjusted in patients with renal impairment (see CLINICAL PHARMACOLOGY – Pharmacokinetics).

Reproductive Health: Female and Male Potential

- **Function**

  There is no information available on teratogenicity of human insulin products.

- **Reproduction**

  There is no information available on teratogenicity of human insulin products.

Transferring Patients from Other Insulins

When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may have changed or become less pronounced than

those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g. regular, NPH or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral anti-diabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first weeks or months and under medical supervision.

Any patient on a total daily dose of greater than 100 units of insulin may need to be closely monitored by the physician when transferring to a different insulin preparation, preferably in hospital.

7.1 Special Populations

7.1.1 Pregnant Women

During pregnancy and lactation, diabetes may become more difficult to manage. However, optimal metabolic control not only during pregnancy, but also prior to conception has proven to be beneficial in reducing the risk of miscarriage and malformation of the fetus. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. Diabetics who have become pregnant or desiring to become pregnant should consult their doctor for advice. Insulin ingested with the mother's milk has not been associated with any risk for the baby.

7.1.2 Breast-feeding

There are no restrictions on the treatment of diabetes with Myxredlin during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the dosage of Myxredlin and/or diet may need to be adjusted.

7.1.3 Pediatrics

No data available to Health Canada.

7.1.4 Geriatrics

No data available to Health Canada.

Others
The presence of diseases such as Acromegaly, Cushing's syndrome, Hyperthyroidism and Pheochromocytoma can complicate the control of diabetes mellitus.

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Myxredlin to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.1 Adverse Reaction Overview

At institution of insulin therapy, oedema and refraction anomalies may occur. These conditions are usually of a transitory nature.

Hypoglycemia is the most frequent undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimes. Therefore, no specific frequency can be presented. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events were reported in three comparative studies performed with the reference biologic drug Novolin®**ge**. In one study, one patient in the Novolin®**ge** treatment group experienced pain at the injection site. In one study, two patients in the Novolin®**ge** treatment group had suspected insulin allergy. However, skin tests showed no evidence of a response to either Novolin®**ge** or Novolin®, Insulin Human Semi-synthetic (ss). One patient receiving Novolin®**ge** was hospitalized with mild ketoacidosis but fully recovered after hospital treatment. In one study seven patients receiving Novolin®**ge** and two Novolin® (ss) reported headaches. There was no clear etiology for these. In addition, eight patients receiving Novolin®**ge** and one receiving Novolin® (ss) experienced pain and burning after injection. These latter findings are difficult to interpret as they are currently seen in clinical practice. They were not related to insulin allergy except in one patient who tested positive to protamine.

8.3 Less Common Clinical Trial Adverse Reactions

No clinical trials, where human insulin has been used as the primary investigational medicinal products (IMP), have been conducted recently. However, human insulin has been used as comparator or concomitant medication in clinical trials where other products have been the IMP.

The overall profile of adverse events – frequency, severity or type of adverse events – reported on human insulin during these clinical trials, has not caused any safety concern. No specific clustering of less common adverse drug reactions have been seen and no changes to the core safety information have been necessary for safety reasons.

8.5 Post-Market Adverse Reactions

The following are adverse drug reactions based on post-marketing experience.

Metabolism and Nutrition Disorders
Rare (<1/1000)
Change in blood glucose: hypoglycemia / hyperglycemia.

Hypoglycemia:
Symptoms of hypoglycemia usually occur suddenly. They may include cold sweats; cool pale skin; fatigue; nervousness or tremor; anxiousness; unusual tiredness or weakness; confusion; difficulty in concentration; drowsiness; excessive hunger; vision changes; headache; nausea and palpitation.

Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Hyperglycemia:
Usually the first symptoms of hyperglycemia set in gradually, over a period of hours or days. They include thirst; increased frequency of urination; nausea; vomiting; drowsiness; flushed dry skin; dry mouth; loss of appetite as well as acetone odour of breath.

In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis which is potentially lethal.

Immune system disorder
Uncommon (>1/1000, <1/100) – Urticaria, rash. Very
rare (<1/10 000) – Anaphylactic reactions.
Symptoms of generalized hypersensitivity may include generalized skin rash; itching; sweating; gastrointestinal upset; angioneurotic oedema; difficulties in breathing; palpitation; reduction in blood pressure and fainting/loss of consciousness. Generalized hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Uncommon (>1/1000, <1/100) – Peripheral neuropathy.

Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

Eye disorders
Very rare (<1/10 000) – Diabetic retinopathy.
Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

Uncommon (>1/1000, <1/100) – Refraction disorders.
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually transitory in nature.

Skin and subcutaneous tissue disorders
Uncommon (>1/1000, <1/100) – Lipodystrophy.
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Uncommon (>1/1000, <1/100) - Injection site reactions.
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are usually transitory and disappear during continued treatment.

Uncommon (>1/1000, <1/100) – Oedema.
Oedema may occur upon initiation of insulin therapy. These symptoms are usually transitory in nature.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

As with insulin in general, concomitant use of other drugs may influence insulin requirements.

9.4 Drug-Drug Interactions

The following substances may reduce the insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulphonamides and alcohol.

The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.

Octreotide/lanreotide may either increase or decrease insulin requirements. Alcohol may

intensify or reduce the hypoglycemic effect of insulin.

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

9.5 Drug-Food Interactions

Please refer to CLINICAL PHARMACOLOGY, Mechanism of Action and DOSAGE AND ADMINISTRATION for interactions with food and timing of food consumption, respectively.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Changes in insulin therapy or changes in lifestyle (i.e. diet, exercise/physical activity) may require a change in dosage.

Patients should be informed about the potential advantages and disadvantages of Myxredlin therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using Myxredlin to obtain optimal glycemic control.

Female patients should be advised to discuss with their physician if they intend to or if they become pregnant.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The primary activity of Myxredlin is the regulation of glucose metabolism. The blood glucose lowering effect of insulins, including Myxredlin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

10.2 Pharmacodynamics

Myxredlin is a fast-acting insulin which is administered by intravenous infusion.
In a double-blind, randomized, crossover, euglycemic glucose clamp study (see COMPARATIVE BIOAVAILABILITY STUDIES), the average onset of action, defined as start of intravenous glucose infusion during the clamp, was approximately 18.5 minutes, after initiation of the intravenous infusion administration. The glucose infusion rate gradually increased to a maximum response of 12.7 mg/kg/min after 5.4 hours of human insulin infusion (see PHARMACOKINETICS).

10.3 Pharmacokinetics

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin is therefore affected by significant intra- and inter-individual variation.

Absorption

In comparison to subcutaneously administered insulin which have a peak insulin effect between 1.5 and 2.5 hours post dose, serum insulin concentrations increase rapidly immediately upon administration by intravenous infusion.

Distribution:

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism:

Human insulin is reported to be degraded by insulin protease or insulin -degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination

Following cessation of intravenous infusion, serum insulin concentration decreases with a median half-life of 29 minutes.

Special Populations and Conditions

No specific pharmacokinetic data on Myxredlin in special patient populations are available. The approved indication covers "Treatment of insulin requiring diabetics" (see *Indications and Clinical* use) without any restrictions regarding age, gender or ethnicity of the diabetes patients.

Dosage is individual and is determined by the physician in accordance with the needs of the patients. However, renal or hepatic impairment may reduce insulin requirements.

Detailed Pharmacology

Animal Pharmacology

The reference biologic drug, Novolin®ge, Insulin, Human Biosynthetic was tested in a number of pharmacological models in order to exclude secondary effects different from those which could be expected with Novolin®, Insulin, Human Semi-synthetic (ss). In a similar series of tests, Novolin® (ss) was compared with pork insulin of equal purity in doses up to 50 U/kg. The models used for both comparisons covered a wide range of target systems and can be seen in the following table:

Table 2 - Animal pharmacological models tested to exclude secondary effects from Novolin®ge different from those expected with Novolin® (ss).

Target System	**Pharmacological Model**		**Secondary Effects Seen (Yes/No)**	
			Novolin® ge compared with Novolin® (ss)	**Novolin® (ss) compared with pork insulin**
1. Central Nervous System	Mice	Ataxia (animex and rotarod) and narcosis potentiation	Yes	Yes
2. Autonomic Nervous System	Cat	Ganglionic Transmission	No	No
3. Neuromuscular Transmission	Rat	Tibial nerve-gastrocnemius muscle preparation	No	No
4. Cardiovascular	Cat	General Hemodynamics, respiration and ECG	No	No
	Rat (conscious)	Blood pressure	No	No
5. Kidneys	Rat	Diuresis and antidiuresis	No	Yes
6. Liver	Pig	Bromsulfophthalein test	No	No

7. Blood Sugar	Rat	Effects on streptozocin induced diabetes	Yes	Yes
8. Isolated Smooth Muscle Preparations	Guinea-Pig	Illuem stimulated with acetylcholine, histamine, serotonim and nicotine	No	No
	Guinea-Pig	Vas deferens stimulated with noradrenaline (concentration of the insulins 50 U/l)	No	No

When comparing Novolin®**ge** and Novolin® (ss), effects were seen in two of the tests (1 and 7). When comparing Novolin® (ss) and pork insulin, in addition to tests 1 and 7, effects were also seen in test 5. This may be due to the dose given or minor differences in experimental design. In all cases, these effects were the same for the two insulin preparations being compared. In other tests no effects were observed with any of the insulin preparations being compared. The immunogenicity of Novolin®**ge** was compared with Novolin® (ss) insulin. The immunization was performed in rabbits with 20 IU per injection in incomplete Freund's adjuvant. No statistically significant difference between the immunogenicity of Novolin®**ge** and Novolin® (ss) insulins was found.

Human Pharmacology

Owens compared the bioavailability of Novolin-Toronto® semi-synthetic with Novolin®**ge** Toronto, the reference biologic drug, following subcutaneous injection in ten normal male volunteer subjects. The study was undertaken with both U40 and U100 insulin preparations. All subjects participated in four separate study days, approximately one week apart. The subjects received, in random order, 0.1 IU/kg body weight of the following: Novolin®**ge** Toronto 40 IU/ml, Novolin®**ge** Toronto 100 IU/ml, and the equivalent Novolin® (ss) insulin preparations following a ten-hour overnight fast prior to each study day. Only the results from the study with U100 insulin are reviewed. No statistically significant differences were observed in terms of plasma insulin and plasma glucose profiles between the two insulin preparations following subcutaneous injections. Plasma glucose and immunoreactive insulin levels were virtually identical. The two comparative preparations were well tolerated by all subjects and no untoward side effects were reported.

Table 3 - Human pharmacological model tested to exclude secondary effect from Novolin®ge that differ from those expected with Novolin® (ss).

Target System	**Pharmacological Model**		**Secondary Effects Seen (Yes/No)**	
			Novolin® ge compared with Novolin® (ss)	**Novolin® (ss) compared with pork insulin**
Thrombocytes	Man	In vitro aggregation (In this test concentrations up to 7.3 U/mL were used)	No	No

11 STORAGE, STABILITY AND DISPOSAL

Store Myxredlin under refrigeration (2 to 8°C) in the original carton to protect from light. Do not use after the expiration date printed on the carton and container label.

If needed, Myxredlin may be removed from the original carton and stored at room temperature up to 25°C for up to 25 days, but not exceeding the original expiry date. Once stored at room temperature, do not place back in the refrigerator. Discard Myxredlin in accordance with local requirements after 25 days if stored at room temperature.

Do not freeze and do not use Myxredlin if it has been frozen (see SPECIAL HANDLING INSTRUCTIONS).

12 SPECIAL HANDLING INSTRUCTIONS

For single use only. Product should be used immediately after insertion of the infusion set to the bag.

Insulin preparations which have been frozen must not be used.

Insulin solutions should not be used if they do not appear water-clear and colourless.

Do not use Myxredlin if particulate matter or colouration is seen.

Do not use if infusion bag is damaged. In case of leaks, discard in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

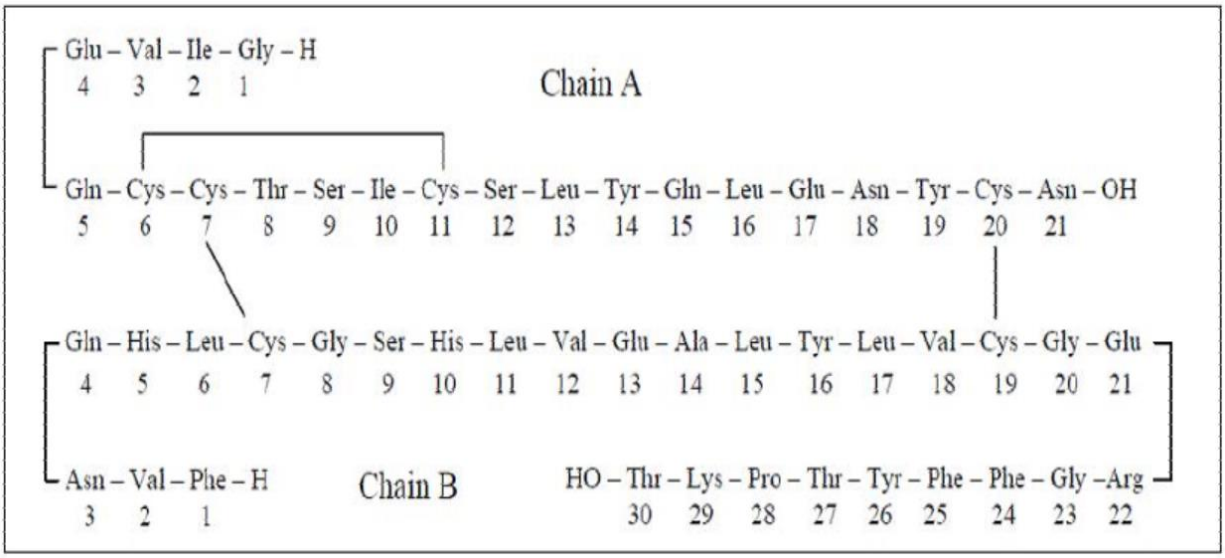
Proper name: Insulin, Human

Chemical name: TBC

Molecular formula and molecular mass: $C_{257}H_{383}N_{65}O_{77}S_6$, approximately 5808 Dalton

Structural formula:

Figure 1. Human insulin - molecular structure.



Physicochemical properties:

Description:
Myxredlin for intravenous use is a sterile, preservative-free, nonpyrogenic, clear, aqueous, and colourless solution supplied in a 100 mL GALAXY single-dose container. It contains 100 units of regular insulin human in 100 milliliters of 0.9% sodium chloride injection. Each milliliter of solution contains 1 unit Insulin Human, USP; 0.412 mg Dibasic Sodium Phosphate Anhydrous, USP; 0.290 mg Monobasic Sodium Phosphate Monohydrate, USP; 9.0 mg Sodium Chloride, USP; and Water for Injection, USP. The pH range is 6.5-7.2.

Pharmaceutical standard:

Insulin Human USP reference standard.

Product Characteristics
Insulin Human is a polypeptide hormone and is produced by recombinant DNA technology, utilizing *Pichia pastoris* (a yeast) as the production organism. During fermentation, the organism secretes a single peptide chain insulin precursor directly into the growth medium. The insulin precursor is then converted to human insulin and subsequently purified to a high degree.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Clinical studies conducted to support similarity between Myxredlin and the reference biologic drug included a double-blinded, randomized comparative bioavailability study performed in healthy adult male subjects.

Study CEL-HI-203 was conducted with Myxredlin and Actrapid (sourced from EU), which was deemed to be an appropriate proxy for the Canadian reference biologic drug, Novolin ge Toronto.

Table 4 - Summary of patient demographics for clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CEL-HI-203	Phase 1, double-blind, randomized, two treatment, two-period, two-way crossover, euglycemic glucose clamp trial	1.0 mU/kg/min, Intravenous, 6 hours (total dose of 0.36 IU/kg)	Normal healthy volunteers; 60 randomized and 54 PK/PD set	33.4 years (19-50 years)	Male

14.2 Study Results

See 14.3 Comparative Bioavailability Studies.

14.3 Comparative Bioavailability Studies

Table 5 - Study CEL-HI-203 – Statistical Analysis of Primary Pharmacokinetic and Pharmacodynamic Parameters
From measured data
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test[1] (N=54)	Reference[2] (N=54)	% Ratio of Geometric Means	Confidence Interval
$AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ (min*pmol/L)	21002.74 21436.48 (20.39)	20328.07 20798.06 (21.95)	103.3	100.23-106.50[3]
$C_{max\ INS\ 300\text{-}360\ min}$ (pmol/L)	390.16 399.13 (21.41)	372.35 380.20 (20.77)	105	101.8-107.9[3]
$AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ (mg)	45855.42 47670.15 (29.48)	44872.15 46722.72 (30.90)	102.0	96.60-107.45[4]

Table 5 - Study CEL-HI-203 – Statistical Analysis of Primary Pharmacokinetic and Pharmacodynamic Parameters
From measured data
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test[1] (N=54)	Reference[2] (N=54)	% Ratio of Geometric Means	Confidence Interval
$GIR_{max\text{-}SS\ 300\text{-}360\ min}$ (mg/min)	941.53 971.11 (26.36)	922.93 947.28 (23.95)	102.5	97.23-107.80[4]

[1] Myxredlin (insulin human in 0.9% sodium chloride injection) by Baxter Corporation
[2] Actrapid (insulin human) (sourced from EU) by Novo Nordisk Limited (as a suitable proxy for the reference biologic drug, Novolin GE Toronto from Novo Nordisk Canada Inc.)
[3] 90% Confidence interval
[4] 95% Confidence interval
Abbreviations: $AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ = area under the insulin concentration-time curve at steady state measured from 300 – 360 minutes, $Cmax_{INS\text{-}SS\ 300\text{-}360\ min}$ = maximal concentration measured at steady state from 300-360 minutes, $AUC_{GIR\text{-}SS,\ 300\text{-}360\ min}$=area under the glucose infusion rate time curve at SS measured from 300 – 360 minutes, $GIR_{max\text{-}SS\ 300\text{-}360\ min}$=maximal glucose infusion rate measured at steady state from 300-360 minutes,.

14.5 Clinical Trials – Reference Biologic Drug

There have been no clinical trials conducted with human insulin since 2002.

Study demographics and trial design

Clinical studies have been designed not only to compare the safety and efficacy of Novolin®**ge** with Novolin® (ss) insulins, but also to screen for the formation of antibodies to *S. cerevisiae.* In order to do this a very sensitive ELISA technique has been developed. Evaluation of sera from 216 healthy volunteers without any history of atopy has been used to establish a normal range for antibodies to yeast and to provide a reference for comparison with samples from clinical trials with Novolin®**ge**.

Fourteen clinical studies investigating the safety and efficacy of Novolin®**ge** have been undertaken. All studies were of twelve months duration. A total of 396 diabetic patients, all previously treated with Novolin® (ss), completed their respective studies. One study was uncontrolled and sequential. Twelve were open, randomized, parallel, asymmetrical comparisons of Novolin®**ge** with the corresponding Novolin® (ss) preparations employing a similar protocol. One study was a multicentre, double blind, randomized, parallel, asymmetrical comparison of Novolin®**ge** with the corresponding Novolin® (ss) preparations.

The safety and efficacy of treatment with a series of premixed preparations of Novolin®**ge** Toronto and Novolin®**ge** NPH was compared with individual mixtures of biosynthetic human insulin manufactured by Eli Lilly in a 12-week crossover study of 38 insulin requiring diabetics. Metabolic control (as judged by HbA1c), 8 point blood glucose profiles (laboratory and home monitored), fasting blood sugar, occurrence and severity of hypoglycemic episodes, and complaints were recorded at predetermined intervals

Study results

No significant differences were found between the two groups for mean 8 point blood glucose profiles (laboratory or home monitored), fasting blood glucose, or the occurrence of hypoglycemic episodes at week 6 or week 12 (crossover and completion). Metabolic control, as judged by HbA1c, remained unchanged between the 2 study groups irrespective of treatment order and no significant differences were found between the 2 groups at week 6 or week 12.

Two studies evaluated the bioequivalence of four different Novolin®**ge** premixed preparations and fresh admixtures of Novolin®**ge** Toronto / Novolin®**ge** NPH of similar proportions in 12 normal volunteers. In each study the serum concentration of immunoreactive insulin, C- peptide and blood glucose were compared after subcutaneous injection of 12 units according to a randomized 4-way crossover design. Bioequivalence was concluded to exist between all four premixed Novolin®**ge** preparations and the comparable admixture of Novolin®**ge** Toronto and Novolin®**ge** NPH as assessed by T_{max}, C_{max}, and AUC.

In both studies some subjects experienced hypoglycemia after administration of insulin especially in the study with Novolin®**ge** 40/60 and Novolin®**ge** 50/50. However, there were no differences between the premixed insulins and the admixtures in this regard. This is not unexpected in view of the proportion of regular insulin given and the fact that the subjects were fasting.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacology and Toxicology

The non-clinical pharmacodynamic and toxicological comparability between Myxredlin and reference biologic drug (Actrapid-EU and/or Novolin R-US) were investigated in *in vitro* and *in vivo* studies. Actrapid-EU (comparable to Novolin R-US) was a suitable proxy for the Canadian reference biologic drug, Novolin ge Toronto.

16.1.1 Comparative Non-Clinical Pharmacodynamics

***In vitro* Studies**

The nonclinical pharmacodynamic data package with Myxredlin has investigated the following aspects relative to Actrapid-EU:

- Comparative receptor binding on both human insulin receptors (IR-A and IR-B) including on – off kinetics.
    - Insulin binding studies by surface plasmon resonance (SPR; long and short form)
- Biological activity addressing receptor autophosphorylation and metabolic activity of Insulin:
    - Insulin receptor phosphorylation (IR-A and IR-B)

- Adipogenesis
- Inhibition of lipolysis
- Glucose uptake

- Effects mediated by Insulin-like growth factor-1 (IGF-1) Reactivity with Insulin:
  - IGF-1 receptor binding assay
  - Mitogenic activity

Taken together, the *in vitro* assessment of the pharmacodynamics of Myxredlin showed that the binding profiles to the insulin receptors (IR-A and IR-B) and Insulin-like growth factor 1 (IGF-1) receptor, biological activity (adipogenesis, inhibition of lipolysis and glucose uptake), and mitogenic activity were similar relative to the reference biologic drug.

16.1.2 Comparative Toxicology

A comparative 14-day continuous intravenous infusion rat toxicology study (including toxicokinetic analysis) was conducted with Myxredlin containing up to 10% desamido insulin-related substances and the reference biologic drug (Novolin R-US, Insulin Human 100 U/mL).

Rats administered Myxredlin with up to 10% desamido insulin-related substances did not show any unique toxicology findings when compared to rats administered reference biologic drug.

16.2 NON-CLINICAL TOXICOLOGY – Reference Biologic

General Toxicology

Table 6 - Details of Animal Toxicity Studies.

	Animal Species			
	Mice and Rats	**Rats**	**Rabbits**	**Beagles**
Objective	Compare Novolin®ge (Insulin, Human Biosynthetic) with Novolin®(ss) (Insulin, Human Semi- synthetic) insulin	Compare Insulin, Human Biosynthetic with Insulin, Human Semi-synthetic		Inject 3.0 U/kg/day over a 13 week period.
Route	Subcutaneous	Subcutaneous	Intermuscular injection	Subcutaneous Injection
Dosage Regimen	Acute	4 week		13 week Period

Results	No differences observed between Insulin, Human Biosynthetic and Insulin, Human Semi- synthetic	No differences observed between Insulin, Human Biosynthetic and Insulin, Human Semi- synthetic		No evidence of toxicity

Local irritation in rabbits after intermuscular injection with Insulin, Human Biosynthetic was similar to that caused by isotonic saline.

Insulin, Human Biosynthetic has been shown to be pyrogen free.

Carcinogenicity
Preclinical data with Insulin, Human Biosynthetic reveal no special hazard for humans based on conventional studies of carcinogenic potential.

Genotoxicity
In a series of sensitive tests designed to evaluate mutagenic Insulin, Human Biosynthetic activity has been shown to be non-mutagenic. Preclinical data with Insulin, Human Biosynthetic reveal no special hazard for humans based on conventional studies of genotoxicity.

17 SUPPORTING PRODUCT MONOGRAPHS

1- Novolin®ge (Insulin, Human Biosynthetic), Injectable Solution/Suspension, Submission Control Number 251302, Product Monograph, Novo Nordisk Canada, August 12, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MYXREDLIN

Insulin Human in 0.9% Sodium Chloride Injection

Sterile Solution for Intravenous Infusion

Read this carefully before you start taking **Myxredlin** 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 **Myxredlin**.

This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist. If you have trouble reading this, ask a family member or a friend for help.

Myxredlin is a biosimilar biologic drug (biosimilar) to the reference biologic drug NOVOLIN® ge Toronto. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin including Myxredlin.
- If hypoglycemic or hyperglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Myxredlin should not be used if it is not clear and colourless.

What is Myxredlin used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).
- Myxredlin, administered intravenously, may be used for the treatment of emergencies, such as diabetic coma and pre-coma, and in diabetics undergoing surgery.

How does Myxredlin work?

Myxredlin is human insulin used to treat diabetes.

What are the ingredients in Myxredlin?

Medicinal ingredients: The active ingredient is Insulin Human which is produced by recombinant DNA methods using a yeast (*Pichia pastoris*) and followed by unique purification processes. Human Insulin is structurally identical to natural human insulin.

Non-medicinal ingredients: Dibasic Sodium Phosphate Anhydrous, Monobasic Sodium Phosphate Monohydrate, Sodium Chloride and Water for Injection.

Myxredlin comes in the following dosage forms:

Myxredlin is presented as a ready-to-use solution for infusion supplied in 100 ml plastic bags. Each mL contains 1 IU of Insulin Human.

Do not use Myxredlin if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see 'What are possible side effects from using Myxredlin?' for more about hypoglycemia).
- You are allergic (hypersensitive) to Insulin, Human Biosynthetic, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see 'What are possible side effects from using Myxredlin?').
- The insulin has not been stored correctly or if it has been frozen (see 'How to store Myxredlin?').
- The insulin does not appear water-clear and colourless.

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

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) watch for signs your need for insulin may change as your blood sugar level may rise or fall.
- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemia coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypoglycemic reactions or if you find it hard to recognize hypoglycemias.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

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).

Other warnings you should know about:

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

- Other medicines for the treatment of diabetes.
- Monoamine oxidase inhibitors (MAOI) (used to treat depression).
- Beta-blockers (used to treat high blood pressure).
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure).
- Salicylates (used to relieve pain and lower fever).
- Anabolic steroids (such as testosterone).
- Sulphonamides (used to treat infections).

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

- Oral contraceptives (birth control pills).
- Thiazides (used to treat high blood pressure or excessive fluid retention).
- Glucocorticoids (such as 'cortisone' used to treat inflammation).
- Thyroid hormones (used to treat thyroid gland disorders).
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma).
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes).
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

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

The following may interact with Myxredlin:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted or thickened area (see 'How to take Myxredlin'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

How to take Myxredlin:

This medicine is given by doctors or nurses in a health care setting. It is given by intravenous infusion, through an injection into a vein.

The doctor decides the number of units to be administered, and for how long, based on your medical needs.

Causes of a hyperglycemia
You get a hyperglycemia if your blood sugar gets too high.

This might happen:

- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Overdose:

Causes of a hypoglycemia
You get a hypoglycemia if your blood sugar gets too low.

This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

The warning signs of a hypoglycemia may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon:

you need to find the reason for your hypoglycemia in order to avoid getting more.

- If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

If you think you, or a person you are caring for, have taken too much Myxredlin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Myxredlin?

These are not all the possible side effects you may have when taking Myxredlin. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, Myxredlin can cause side effects, although not everybody gets them. Myxredlin may cause low blood sugar (hypoglycemia) (see the advice in 'How to take Myxredlin').

Less commonly reported side effects
(1 to 10 users in 1000)

Signs of allergy
Hives and rash may occur.

Seek medical advice immediately

- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to Myxredlin or one of its ingredients (called a generalized allergic reaction) (see also the warning in 'Do not use Myxredlin if').

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

Swollen joints
When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

Painful neuropathy (nerve related pain)
If your blood glucose levels improve very fast it may cause burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

Very rarely reported side effects
(less than 1 in 10,000)

Diabetic retinopathy (eye background changes)

If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects get serious, or if you notice any side effects, including those not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy: hives and rash		√	√
Vision problems	√		
Changes at the injection site (Lipodystrophy)		√	
Swollen joints	√		
Painful neuropathy (nerve related pain)		√	√
RARE (less than 1 in 10,000)			
Diabetic retinopathy (eye background changes)		√	√
UNKNOWN			
Cutaneous Amyloidosis: lumps under skin		√	

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect- canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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:

Do not use this medicine after the expiry date, which is stated on the infusion bag and carton labels

after ‘EXP’. The expiry date refers to the last day of that month.

Before opening, store infusion bag contained within a cardboard carton at 2-8°C. If needed, infusion bag may be removed from the original carton and stored at room temperature (up to 25°C) for up to 25 days, but not exceeding the original expiry date.

After opening, the product should be used immediately. Any unused solution should be discarded in accordance with local requirements.

Do not use this medicinal product if you notice that the solution is not clear, and colourless.

Do not use if the infusion bag is damaged. In case of leaks, discard in accordance with local requirements.

Do not use this medicinal product if has been frozen

Keep out of reach and sight of children.

If you want more information about Myxredlin:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug- products/drug-product-database.html; the manufacturer’s website www.baxter.ca or by calling 1-800-719-9955.

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