PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrINCRELEX®

mecasermin injection

10 mg/mL (40 mg/4mL)

Recombinant DNA-derived human insulin-like growth factor-1 (IGF-1)

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.4 Administration	04/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Increlex® (mecasermin) is indicated for the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD). SPIGFD is defined by:

- height standard deviation score ≤ –3.0 and;
- basal IGF-1 levels below the 2.5th percentile for age and gender and;
- GH sufficiency.
- Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

SPIGFD includes patients with mutations in the GH receptor (GHR) gene/Laron's syndrome, post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

1.1 Pediatrics

Pediatrics (2-18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Increlex in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. The safety and efficacy of Increlex in children below the age of 2 have not been established and therefore Increlex is not recommended in children below the age of 2 (See WARNINGS AND PRECAUTIONS, Benzyl alcohol toxicity).

2 CONTRAINDICATIONS

Increlex (mecasermin) 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.
- Children and adolescents with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia.
- Increlex contains benzyl alcohol and must not be given to premature babies or neonates.
- Increlex should not be used for growth promotion in patients with closed epiphyses.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment with Increlex (mecasermin) should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.
- The dose should be tailored specifically for each patient and should be adjusted based on tolerability and weight. If a child's weight changes, the dose should be adjusted to maintain a consistent mg/kg dosage.
- Preprandial glucose monitoring is recommended at treatment initiation and until a well-tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue.

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Increlex is 0.04 to 0.08 mg/kg (40 to 80 mcg/kg) twice daily by subcutaneous injection. If Increlex is well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose to the maximum dose of 0.12 mg/kg given twice daily.

Doses greater than 0.12 mg/kg twice daily should not be exceeded as this may increase the risk of neoplasia and hypoglycemic effects (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

If the recommended dose is not tolerated by the patient, treatment with a lower dose can be considered. Treatment success should be evaluated based on height velocities. The lowest dose that was associated with substantial growth increases on an individual basis was 0.04 mg/kg BID.

4.4 Administration

Increlex is administered by subcutaneous injection. Increlex should not be administered intravenously. Increlex injection sites should be rotated to a different site (upper arm, thigh, buttock or abdomen) with each injection to help prevent lipohypertrophy. Increlex should be administered using sterile disposable syringes and needles.

The syringes should be of small enough volume so that the prescribed dose can be withdrawn from the vial with accuracy. If using syringes that measure dose in units, doses in mg/kg must be converted to units using the following formula: Weight (kg) x Dose (mg/kg) x 1 mL/10 mg x 100 units/1 mL = units/injection.

Increlex should be administered by subcutaneous injection shortly before or after a meal or snack. If hypoglycemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat, for any reason, this medicinal product should be withheld and re-introduced when the patient is able to eat normally.

4.5 Missed Dose

The dose of Increlex should never be increased to make up for one or more missed doses.

5 OVERDOSAGE

Acute overdose could lead to hypoglycemia. Treatment of acute overdose should be directed at reversing hypoglycemia. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous (IV) glucose or parenteral glucagon may be required to reverse the hypoglycemic effects.

Long-term overdose may result in signs and symptoms of acromegaly or gigantism. Overdosing may lead to supraphysiological IGF-1 levels and may increase the risk of benign and malignant neoplasm.

In case of an acute or a chronic overdose, Increlex must be discontinued immediately. If Increlex is restarted, the dose should not exceed the recommended daily dosage (see Recommended Dose and Dosage Adjustment).

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, health professionals should recognize 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
Subcutaneous Injection	Sterile solution 10 mg/mL (40 mg per vial)	Benzyl alcohol, sodium chloride, polysorbate 20, glacial acetic acid, sodium acetate trihydrate, water for injection.

Increlex is supplied in a 5 ml multi-dose vial (type I glass) closed with a stopper (chloro-butyl/isoprene polymer) and a seal (coloured plastic). Each vial contains 4 ml of solution. Pack size of 1 vial.

7 WARNINGS AND PRECAUTIONS

General
Increlex is not a substitute for GH treatment.

Carcinogenesis and Mutagenesis
There is an increased risk of benign and malignant neoplasia in children and adolescents treated with Increlex, since IGF-1 plays a role in the initiation and progression of benign and malignant tumors (see CONTRAINDICATIONS).

There have been post-marketing reports of both benign and malignant neoplasms in children and adolescents who have received treatment with Increlex. These cases represented a variety of different malignancies and included rare malignancies usually not seen in children (see ADVERSE REACTIONS, Neoplasms and Post-Market Adverse Reactions). The increased risk

of neoplasia may be higher in patients who receive Increlex for unapproved uses, at higher than recommended doses or at doses that produced serum IGF-1 levels above the normal reference ranges for age and sex. Current knowledge of IGF-1 biology suggests that IGF-1 plays a role in malignancies in all organs and tissues. Physicians should therefore be vigilant of any symptoms of potential malignancy. Advise patients/caregivers to report development of new neoplasms. If benign or malignant neoplasia develops, Increlex treatment should be discontinued definitely and appropriate expert medical care sought.

Driving and Operating Machinery
Increlex may cause hypoglycemia (very common side effect), dizziness and convulsions (see ADVERSE REACTIONS, Hypoglycemia) that may impair your ability to drive and use machines.

You should avoid engaging in any high-risk activities (e.g., driving, using machines, etc.) within 2-3 hours after dosing, particularly during the initiation of Increlex treatment until tolerability and a stable dose have been established.

Ear/Nose/Throat
Lymphoid tissue (e.g., tonsillar) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of Increlex. Patients should have examinations periodically and at the occurrence of clinical symptoms to rule out such potential complications or to initiate appropriate treatment (see ADVERSE REACTIONS, Tonsillar hypertrophy and snoring).

Endocrine and Metabolism
Hypoglycemia
Increlex should be administered shortly before or after a meal or snack, because it may have insulin-like hypoglycemic effects. Glucose monitoring and Increlex dose titration are recommended until a well-tolerated dose is established (see DOSAGE AND ADMINISTRATION). Increlex should not be administered when a meal or snack is omitted. The dose of Increlex should never be increased to make up for one or more omitted doses. Special attention should be paid to young children, children with a history of hypoglycemia and children with inconsistent food intake. Patients should avoid engaging in any high-risk activities within 2-3 hours after dosing, particularly at the initiation of Increlex treatment, until a well-tolerated dose of Increlex has been established.

If a person with severe hypoglycemia is unconscious or otherwise unable to ingest food normally, an injection of glucagon may be required. Persons with a history of severe hypoglycemia should have glucagon available. At the time of initial prescription, physicians should educate parents on the signs, symptoms and treatment of hypoglycemia, including injection of glucagon.

Doses of insulin and/or other hypoglycemic medicinal products may need to be reduced for diabetic subjects using this medicinal product.

Bone Metabolism
Slipped capital femoral epiphysis (with the potential to lead to avascular necrosis) and progression of scoliosis can occur in patients who experience rapid growth. These conditions and other symptoms and signs known to be associated with GH treatment in general should be monitored during Increlex treatment. Any patient with the onset of a limp or complaint of hip or knee pain should be evaluated. Patients with a history of scoliosis who are treated with Increlex should be monitored for progression of scoliosis.

Immune

Systemic/local hypersensitivity

Allergic reactions to Increlex have been reported in clinical trials and post-marketing experience. They range from localized (injection site) reactions (e.g., urticaria, pruritus, erythema) to systemic reactions, including anaphylaxis, generalized urticaria, angioedema and dyspnea. Some patients required hospitalization. Parents and patients should be informed that such reactions are possible and that if a systemic allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought (see CONTRAINDICATIONS, ADVERSE REACTIONS, Hypersensitivity and Post-Market Adverse Reactions, Systemic hypersensitivity).

Monitoring and Laboratory Tests

Echocardiogram is recommended before initiation of Increlex treatment in all patients and in patients who terminate treatment. Patients with abnormal echocardiogram findings or cardiovascular symptoms should be followed regularly with echocardiogram procedures (see ADVERSE REACTIONS, Organomegaly).

Neurologic

Intracranial hypertension

Intracranial hypertension (IH) with papilloedema, visual changes, headache, nausea and/or vomiting has been reported in patients treated with Increlex, as has been reported with therapeutic GH administration. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination is recommended at the initiation, periodically during the course of Increlex therapy and at the occurrence of clinical symptoms (see ADVERSE RECTIONS, Intracranial hypertension).

Others

Benzyl alcohol toxicity

Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children. Serious and fatal adverse reactions including "gasping syndrome" can occur in premature/low-birth weight neonates, neonates and infants who received drugs containing benzyl alcohol in any amount as a preservative, including Increlex. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

Use of Increlex in premature infants, neonates and children below the age of 2 is not authorized (see INDICATIONS and CONTRAINDICATIONS).

Sensitivity/Resistance

Persons who have allergic reactions to injected IGF-1, who have unexpectedly high blood values of IGF-1 after injection, or who fail to show a growth response without any identified cause may be having an antibody response to injected IGF-1. This may be through the production of anti-IGF-1 IgEs, sustaining antibodies or neutralizing antibodies respectively. In such instances, instructions for antibody testing should be considered.

Reproductive Health: Female and Male Potential
Fertility
The effects of mecasermin on fertility in humans have not been studied.

7.1 Special Populations

7.1.1 Pregnant Women

A negative pregnancy test is recommended for females of child bearing potential prior to treatment with Increlex. It is also recommended that all women of childbearing potential use adequate contraception during treatment.

There are no data for the use of mecasermin in pregnant women. In an embryo-fetal development study conducted with pregnant rabbits, IV administration of mecasermin during organogenesis reduced fetal viability (see NON-CLINICAL TOXICOLOGY). The potential risk for humans is unknown. This medicinal product should not be used during pregnancy unless clearly necessary.

7.1.2 Breast-feeding

Breast-feeding while taking Increlex is not recommended, because there is insufficient information on the excretion of mecasermin in human milk.

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Increlex in pediatric patients (2-18 years of age) has been established; therefore, Health Canada has authorized an indication for pediatric use. The safety and efficacy of Increlex in children below the age of 2 have not been established.

7.1.4 Geriatrics

The safety and effectiveness of Increlex in patients aged 65 and over has not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Data from 4 predecessor studies and the pivotal study 1419 were pooled for safety analyses and formed the integrated safety database, which included a total of 92 children with SPIGFD who received at least one dose of Increlex. The most common treatment emergent adverse events (TEAEs) were hypoglycemia (43 subjects (47%)), hypersensitivity (33 subjects (35%)), injection site hypertrophy (32 subjects (35%)), headache (25 subjects (27%)) and snoring (20 subjects (22%)). Seventy-six subjects (83%) had at least one reported TEAE during treatment. Eighteen subjects (20%) experienced at least one serious adverse event. The most common SAEs reported were tonsillar hypertrophy and adenoidal hypertrophy in 6 (6.5%) subjects. There were no deaths reported. No patient discontinued the treatment due to AEs. Hypoglycemia was the most frequently reported AE.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 summarises adverse reactions that occurred in ≥1% of patients in pivotal study 1419.

Table 2 – Adverse Reactions* Occurring in ≥ 1% of Increlex Treated Patients in Pivotal Study 1419

	Increlex n = 92 n (%)
Blood and Lymphatic Disorders	
Thymus hypertrophy	9 (10)
Cardiac Disorders	
Cardiac murmur	7 (8)
Tachycardia	6 (7)
Ear and Labyrinth Disorders	
Hypoacusis[a]	19 (21)
Middle ear effusion	10 (11)
Ear pain	6 (7)
Ear discomfort	5 (5)
Eye Disorders	
Papilloedema	5 (5)
Gastrointestinal Disorders	
Vomiting	16 (17)
Abdominal pain	8 (9)
Upper abdominal pain	5 (5)
General Disorders and Administration Site Conditions	
Injection site hypertrophy	32 (35)
Injection site reactions[b]	18 (19)
Hypertrophy	8 (9)
Immune system disorders	
Hypersensitivity[c]	33 (35)
Infection and Infestations	
Otitis media	19 (21)
Investigations	
Increased weight	3 (3)
Metabolism and Nutrition Disorders	
Hypoglycemia[d]	43 (47)
Hypoglycemic seizure	7 (7)
Hyperglycemia	4 (4)

	Increlex n = 92 n (%)
Musculoskeletal and Connective Tissue	
Arthralgia	8 (9)
Pain in extremity	8 (9)
Myalgia	2 (2)
Scoliosis	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Melanocytic nevus	4 (4)
Acrochordon	3 (3)
Skin papilloma	2 (2)
Nervous System Disorders	
Headache	25 (27)
Intracranial hypertension[e]	6 (7)
Dizziness	6 (7)
Convulsions	4 (4)
Tremor	1 (1)
Respiratory, Thoracic, and Mediastinal	
Snoring	20 (22)
Tonsillar hypertrophy	19 (21)
Adenoidal hypertrophy	9 (10)
Sleep apnea syndrome	3 (3)
Reproductive system and breast disorders	
Gynecomastia	6 (7)
Skin and Subcutaneous Tissue Disorders	
Skin hypertrophy	10 (11)
Abnormal hair texture	4 (4)

*Derived from treatment-emergent adverse events
[a]includes hypoacusis, conductive deafness and deafness.
[b]includes injection site bruising, injection site pain, injection site reaction, injection site hematoma, injection site induration and injection site hemorrhage.
[c]includes cough, rash, dyspnea, pruritic rash, drug hypersensitivity, hypersensitivity, pruritus, asthma, urticaria and injection site urticaria.
[d]formerly hypoglycemia NOS
[e]includes papilloedema

Description of Selected Adverse Reactions

Neoplasms

In Study 1419, 7 subjects (8%) reported benign neoplasms.

Hypoglycemia

In Study 1419, 43 subjects (47%) experienced one or more episodes of hypoglycemia during treatment of Increlex. Seven (8%) subjects had severe hypoglycemia (requiring assistance and treatment) and 7 (7%) experienced hypoglycemic seizures/loss of consciousness on one or more occasions. The frequency of hypoglycemia was highest in the first month of treatment, and episodes were more frequent in younger children (see WARNINGS AND PRECAUTIONS,

Hypoglycemia).

Hypersensitivity
In Study 1419, 33 subjects (35%) reported a local and/or systemic hypersensitivity reaction, including cough, rash, dyspnea, pruritic rash, drug hypersensitivity, hypersensitivity, pruritus, asthma, urticaria and injection site urticaria (see WARNINGS AND PRECAUTIONS, Systemic/local hypersensitivity and Post-Market Adverse Reactions, Systemic hypersensitivity).

Intracranial hypertension (IH)/increased intracranial pressure
In Study 1419, IH (i.e, papilloedema and benign IH) and headache occurred in 6 subjects (7%) and 25 subjects (27%), respectively. One subject had severe benign IH classed as a related SAE. In post-marketing experience, 2 intracranial hypertension events were life threatening and involved hospitalisation (see WARNINGS AND PRECAUTIONS, Intracranial hypertension).

Injection site hypertrophy
In Study 1419, injection site hypertrophy occurred in 32 (35%) subjects and was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved.

Tonsillar hypertrophy and snoring
In Study 1419, tonsillar hypertrophy was noted in 19 (21%) subjects, particularly in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years. Snoring occurred generally in the first year of treatment and was reported in 20 subjects (22%).

Organomegaly
Echocardiographic evidence of cardiomegaly/valvulopathy was observed in a few individuals without associated clinical symptoms. The relation of these cardiac changes to drug treatment cannot be assessed due to underlying disease and the lack of a control group (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Thickening of the soft tissues of the face was observed in several patients and should be monitored during Increlex treatment.

Renal and splenic lengths (measured by ultrasound) increased rapidly on Increlex treatment during the first years of therapy. This lengthening slowed down subsequently; though in some patients, renal and/or splenic length reached or surpassed the 95th percentile.

Immunogenicity
The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Anti-IGF-1 antibodies were only analyzed in 23 out of 92 patients in the predecessor studies of the integrated Study 1419 during the first year of treatment. Of the 23 patients, 11 patients tested positive for anti-IGF-1 antibodies. Neutralizing antibodies were not analyzed in Study 1419. The impact of anti-IGF-1 antibodies on pharmacokinetics was not investigated. The mean (SD) height velocities were 7.9 ± 2.1 cm/year in patients with anti-IGF-1 antibodies (n=11), and 7.1 ± 3.0 cm/year in patients without anti-IGF-1 antibodies (n = 12).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings
Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment. Rise in levels of these serum enzymes did not lead to treatment discontinuation. ALT elevations were occasionally noted during treatment.
Elevations in cholesterol and triglycerides to above the upper limit of normal were observed before and during treatment.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of Increlex. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Cardiac Disorders: cardiomegaly

Systemic hypersensitivity: anaphylaxis, generalized urticaria, angioedema, dyspnea
In the post-marketing setting, the frequency of cases indicative of anaphylaxis was estimated to be 0.3%. Symptoms included hives, angioedema, and dyspnea, and some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients.

Local allergic reactions at the injection site: pruritus, urticaria

Skin and Subcutaneous Tissue Disorders: alopecia, hair texture abnormal

General Disorders and Administrative Site Conditions: injection site reactions (e.g. erythema, pain, hematoma, hemorrhage, induration, rash, swelling)

Musculoskeletal and Connective Tissue Disorders: osteonecrosis/avascular necrosis (occasionally associated with slipped capital femoral epiphysis)

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) : benign and malignant neoplasms. See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS. In post-marketing experience, 42 cases of neoplasms benign, malignant and unspecified (including cysts and polyps) were reported, including 23 benign neoplasia and 19 malignant neoplasia cases.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed.

Doses of insulin and/or other hypoglycemic medicinal products may need to be reduced (see WARNINGS AND PRECAUTIONS).

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

IGF-1 is a key hormonal mediator on statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver, and other tissues, and stimulates the synthesis/secretion of IGF-1. In target tissues, the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes resulting in statural growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

10.2 Pharmacodynamics

The following actions have been demonstrated for endogenous human IGF-1:

Tissue Growth
Skeletal growth occurs at the cartilage growth plates of the epiphyses of bones where stem cells divide to produce new cartilage cells or chondrocytes. The growth of chondrocytes is under the control of IGF-1 and GH. The chondrocytes become calcified so that new bone is formed allowing the length of the bones to increase. This results in skeletal growth until the cartilage growth plates fuse at the end of puberty.
Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activities that lead to an increased number of cells in the body.
Organ growth: Treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Carbohydrate Metabolism
IGF-1 suppresses hepatic glucose production and stimulates peripheral glucose utilization and therefore has a hypoglycemic potential. IGF-1 has inhibitory effects on insulin secretion.

10.3 Pharmacokinetics

Mecasermin exhibited non-linear pharmacokinetics with exposure increased less than

proportionally with doses over the range of 0.015 mg/kg – 0.12 mg/kg in subjects with primary IGFD.

Table 3 – Summary of Mecasermin Single Dose Pharmacokinetic Parameters in Subjects (age: 14-18 years) with Severe Primary IGFD (0.12 mg/kg, SC, n = 3)

	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (h)	$AUC_{0-\infty}$ (hr*ng/mL)	CL/F (L/hr/kg)	Vd/F (L/kg)
Single Dose Mean	234	2	5.8	2932	0.053	0.31
CV%	23	0	64	50	69	27

CV% = coefficient of variation in %.
Pharmacokinetic parameters based on baseline adjusted plasma concentrations.

Absorption: The absolute bioavailability of mecasermin after subcutaneous administration in healthy subjects is estimated to be close to 100% based on cross-study comparison. However, the absolute bioavailability of mecasermin given subcutaneously to subjects with primary IGFD has not been determined. Following subcutaneous administration of 0.04, 0.08 or 0.12 mg/kg mecasermin twice daily in pediatric subjects, the steady state was achieved by approximately 4 days with accumulation ratio of approximately 1.1-1.5, based on population PK analysis.

Distribution: In blood, IGF-1 is bound to six IGF binding proteins, with > 80% bound as a complex with IGF binding protein-3 (IGFBP-3) and an acid-labile subunit. IGFBP-3 is greatly reduced in subjects with SPIGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects. Based on population pharmacokinetic analysis, the total IGF-1 volume of distribution after subcutaneous administration in subjects with SPIGFD is estimated to increase as the dose of mecasermin increases.

Metabolism: IGF-1 is metabolized by both the liver and kidney.

Elimination: The mean terminal $t_{1/2}$ after single subcutaneous administration of 0.12 mg/kg mecasermin in pediatric subjects with SPIGFD is estimated to be 5.8 (CV 64%) hours. Clearance of mecasermin is inversely proportional to IGFBP-3 levels, and CL/F is estimated to be 0.045 L/hr/kg at 0.5 mcg/mL of IGFBP-3 in subjects with SPIGFD, based on population pharmacokinetic analysis.

Special Populations and Conditions

Geriatrics*:* No formal clinical trials of mecasermin were conducted to include geriatric subjects (≥ 65 years).

Sex: In adolescents with primary IGFD there were no apparent differences between males and females in the pharmacokinetics of mecasermin.

Ethnic origin: The effect of race on pharmacokinetics of mecasermin has not been studied.

Hepatic Insufficiency*:* No specific studies were conducted to determine the effect of hepatic impairment on the pharmacokinetics of mecasermin.

Renal Insufficiency*:* No specific studies were conducted to determine the effect of renal impairment on the pharmacokinetics of mecasermin.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C - 8°C). Do not freeze. The solution should be clear immediately after removal from the refrigerator. If the solution is cloudy, or contains particulate matter, it must not be injected.

Keep the vial in the outer carton in order to protect from light.

Chemical and physical in-use stability has been demonstrated for 30 days at 2°C to 8°C. From a microbiological point of view, once opened, the medicinal product may be stored for a maximum of 30 days at 2°C to 8°C.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

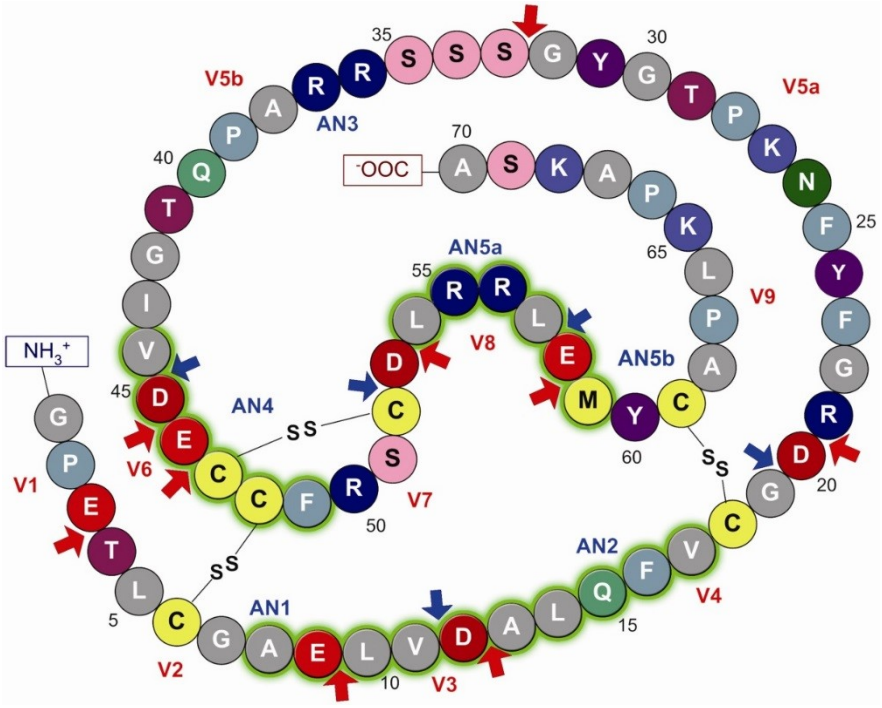
Proper name: mecasermin

Chemical name: Recombinant human Insulin-like Growth Factor-1 (rhIGF-1)

Molecular formula and molecular mass: $C_{331}H_{512}N_{94}O_{101}S_7$, 7649 Daltons

Increlex (mecasermin) injection contains human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges and a molecular weight of 7649 daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The rhIGF-1 protein is synthesized in bacteria (E. coli) that have been modified by the addition of the gene for human IGF-1.

Structural formula:



Physicochemical properties: rhIGF-1 is a single-chain, non-glycosylated basic polypeptide stabilized with 3 intra-chain disulfide bonds. It has a molar absorptivity of 0.645 (mL/mg)/cm at 276 nm and a pI of 8.65. It is readily soluble in water, and aqueous solutions of rhIGF-1 are clear, colorless and odorless.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 – Summary of Study Design and Patient Demographics for the Pivotal Clinical Trial in SPIGFD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
1419	Pooled findings from five clinical studies (four open-label and one double-blind, placebo-controlled)	Subcutaneous BID injections 0.06 to 0.12 mg/kg	n=92 Subjects had growth failure with SPIGFD	Pre-treatment age (years) 1.7-15.2	Male n=46 (57%) Female n=35 (43%)

Study 1419 included 81 treatment-naïve patients with SPIGFD, who completed at least one year of Increlex treatment. Of these, 89% had Laron Syndrome (GHR mutation). At baseline, patients with SPIGFD were severely short with a mean estimated baseline height SD score of -6.9 (range: -12.1 to -2.8), low IGF-1 serum concentrations, and normal GH secretion. The mean pre-treatment height velocity was 2.6 cm per year. The majority were pre-pubertal (n=74), and of Caucasian background (81%), and had a mean chronological age of 6.8 years, whereas the mean bone age was 3.8 years. The safety analysis included 92 patients, who received at least one dose of Increlex.

14.2 Study Results

The results from five clinical studies were pooled for a global efficacy and safety analysis and are presented in table 5. Pre-treatment height velocity information was available from 75 patients. The primary efficacy endpoint was change in height velocity from pre-treatment during each year of treatment in subjects naïve to Increlex.

Table 5 – Annual Height Results by Number of Years Treated with Increlex from Study 1419

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
N	75	75	63	62	60	53	39	25	19
Mean (SD)	2.6	8.0	5.9	5.5	5.2	4.9	4.8	4.3	4.4
	(1.7)	(2.3)	(1.7)	(1.8)	(1.5)	(1.5)	(1.4)	(1.5)	(1.5)
Mean (SD) for		+5.4	+3.2	+2.8	+2.5	+2.1	+1.9	+1.4	+1.3
change from pre-Tx		(2.6)	(2.6)	(2.4)	(2.5)	(2.1)	(2.1)	(2.2)	(2.8)
Height Velocity SDS									

N	75	75	62	61	58	50	37	22	15
Mean (SD)	-3.4	1.7	-0.0	-0.1	-0.2	-0.3	-0.2	-0.5	-0.2
	(1.6)	(2.8)	(1.7)	(1.9)	(1.9)	(1.7)	(1. 6)	(1.7)	(1.6)
Mean (SD) for		+5.2	+3.4	+3.3	+3.2	+3.2	+3.3	+3.0	+3.3
change from pre-Tx		(2.9)	(2.4)	(2.3)	(2.1)	(2.1)	(2.0)	(2.1)	(2.7)
Height SDS									
N	81	81	67	66	64	57	41	26	19
Mean (SD)	-6.9	-6.1	-5.6	-5.3	-5.1	-5.0	-4.9	-4.9	-5.1
	(1.8)	(1.8)	(1.7)	(1.7)	(1.7)	(1.7)	(1.6)	(1.7)	(1.7)
Mean (SD) for		+0.8	+1.2	+1.4	+1.6	+1.7	+1.8	+1.7	+1.7
change from pre-Tx		(0.6)	(0.9)	(1.1)	(1.2)	(1.3)	(1.1)	(1.0)	(1.0)

Pre-Tx = Pre-treatment; SD = Standard Deviation; SDS = Standard Deviation Score

16 NON-CLINICAL TOXICOLOGY

General Toxicology

To assess the repeat-dose toxicity of mecasermin, 6-month toxicity studies involving the SC daily administration of mecasermin were conducted in Sprague Dawley rats (0.25, 1 and 4 mg/kg/day) and Beagle dogs (0.15, 0.3 and 0.6 mg/kg/day). In treated rats, mecasermin was relatively well tolerated following 26 weeks of consecutive treatment at dose levels up to 1.0 mg/kg/day. Clinical pathology and organ weight changes identified primarily at a dose of 4.0 mg/kg/day were generally attributable to direct or indirect effects associated with the known pharmacological activity of mecasermin. At 4.0 mg/kg/day, a reversible change in thymic pathology was noted which corresponded to treatment-related changes in the weight of this organ. The No-Observed-Adverse-Effect-Level (NOAEL) for this study was determined to be 1.0 mg/kg/day (below the maximum recommended human dose [MRHD] based on body surface area). In treated dogs, mecasermin was well tolerated following 26 weeks of consecutive treatment at doses up to 0.15 mg/kg/day. At doses of 0.3 mg/kg/day, adrenal changes were noted (2 out of 6 dogs) and at a dose of 0.6 mg/kg/day, marked toxicity, including death was observed. In general, the effects noted in this study were consistent with the known pharmacological effects and expected glucose lowering activity of mecasermin. For this study, the NOAEL was determined to be 0.15 mg/kg/day (below the MRHD based on AUC or body surface area).

Carcinogenicity

Mecasermin was administered subcutaneously to Sprague Dawley rats at doses of 0, 0.25, 1, 4, and 10 mg/kg/day for up to 2 years. An increased incidence of adrenal medullary hyperplasia and pheochromocytoma was observed in male rats at doses of 1 mg/kg/day and above (below the clinical exposure with the MRHD based on AUC) and female rats at all dose levels (below the clinical exposure with the MRHD based on AUC). An increased incidence of keratoacanthoma in the skin was observed in male rats at doses ≥ 4 mg/kg/day (1.3 times the exposure with the MRHD based on AUC). An increased incidence of mammary gland carcinoma in both male and female rats was observed in animals treated with 10 mg/kg/day (2.4 and 1.7 times for male and female rats, respectively, the exposure with the MRHD based on AUC). Excess mortality secondary to IGF-1 induced hypoglycemia was observed in the carcinogenicity study.

Genotoxicity
No evidence of genotoxicity was observed with mecasermin in a chromosomal aberration test conducted in Chinese hamster lung fibroblasts at concentrations of mecasermin of up to 487 µg/mL or in an *in vivo* mouse micronucleus test employing IV doses of mecasermin up to 97.4 mg/kg.

Reproductive and Developmental Toxicology
Embryo-fetal development studies were conducted with pregnant rats and rabbits in which mecasermin was administered intravenously during the period of organogenesis. No effects on rat fetuses were observed at doses up to 16 mg/kg/day (11-fold the MRHD based on body surface area). However, reduced fetal viability was reported in pregnant rabbits administered 2 mg/kg bw/day. The NOAEL was determined to be 0.5 mg/kg/day in rabbits (below the MRHD based on body surface area). Placental transfer of mecasermin was not studied.

In the fertility study, the male rats were administered using IV doses of 0.25, 1, and 4 mg/kg/day for 9 weeks and the females for 2 weeks prior to the 2-week cohabitation period. Daily dosing continued throughout the cohabitation period and until one week following copulation in males or until Day 7 of gestation for females. Mecasermin has no effects on fertility in rats using IV doses 0.25, 1, and 4 mg/kg/day (up to 3 times the clinical exposure with the MRHD based on AUC).

Due to the different route of application, and the use of a less bioavailable formulation of mecasermin as the test article in these studies, the relevance of these findings is unclear.

Juvenile Toxicity
Juvenile toxicity studies have not been conducted with mecasermin.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Increlex
mecasermin injection

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

What is Increlex used for?

- It is used to treat children and adolescents from 2 to 18 years old who are very short for their age because their bodies do not make enough IGF-1. This condition is called primary IGF-1 deficiency.
- Increlex has not been studied in children younger than 2 years, and it is not known if Increlex is safe and effective in children younger than 2 years. Therefore Increlex should not be used in children below the age of 2.

How does Increlex work?

Increlex is a liquid that contains mecasermin which is a man-made insulin-like growth factor-1 (IGF-1), which is similar to the IGF-1 made by your body.

What are the ingredients in Increlex?

Medicinal ingredients: mecasermin
Non-medicinal ingredients: benzyl alcohol, sodium chloride, polysorbate 20, glacial acetic acid, sodium acetate, trihydrate, water for injection.

Increlex comes in the following dosage forms:

10 mg/mL (40 mg/4mL) solution for injection. Each multi-dose vial contains 40 mg of mecasermin.

Do <u>not</u> use Increlex:

- if you currently have any tumour or growth, either cancerous or non-cancerous
- if you have had cancer in the past
- if you have any conditions which may increase the risk of cancer
- if you are allergic to mecasermin or any of the other ingredients of this medicine (see What are the ingredients in Increlex?)
- in premature babies or neonates because it contains benzyl alcohol
- if you have finished growing (the bone growth plates are closed)

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

- currently have any tumour or abnormal growth, have had cancer in the past or have any conditions which may increase the risk of cancer.
- have diabetes. Tell your doctor if you take insulin or other anti-diabetes medicines. A change in dose may be needed for these medicines.

- have a curved spine (scoliosis). You should be monitored for progression of scoliosis.
- develop a limp or hip or knee pain
- have enlarged tonsils (tonsillar hypertrophy). You should have examinations periodically.
- have symptoms of increased pressure in the brain (intracranial hypertension), such as visual changes, headache, nausea and/or vomiting, contact the doctor for advice.
- have a localised reaction at the injection site or generalised allergic reaction with Increlex.
- have finished growing (the bone growth plates are closed). In this case Increlex cannot help you grow and should not be used.
- are pregnant or breast-feeding, or think you may be pregnant or are planning to have a baby.
    - Increlex should be discontinued if pregnancy occurs.
    - Increlex should not be taken if you are breast-feeding.

Other warnings you should know about:

- **Tumour growths**
  There is a higher risk of tumours (both cancerous and non-cancerous) in children and adolescents treated with Increlex. If any new tumour growth, skin lesion or any unexpected symptom occurs during treatment or after treatment, see your doctor immediately since Increlex may play a role in cancer development.

- **Low blood sugar (Hypoglycemia)**
  Increlex may lower blood sugar levels. Signs of low blood sugar include: dizziness, tiredness, restlessness, hunger, irritability, trouble concentrating, sweating, nausea, fast or irregular heartbeat. It is important to only give Increlex 20 minutes before or 20 minutes after a meal or snack to reduce the chances of low blood sugar. Do NOT give Increlex if you cannot eat.

  If you take Increlex, you should avoid engaging in any high-risk activities (e.g., driving or using machines) within 2-3 hours after dosing, particularly at the start of Increlex treatment.

  Before beginning treatment with Increlex your doctor or nurse will explain to you how to treat hypoglycemia. You should always have a source of sugar such as orange juice, glucose gel, candy, or milk available in case symptoms of hypoglycemia happen.

- **Injection site reactions**
  Increlex can cause injection site hypertrophy (tissue at injection site increases in size), pain, redness, or bruising. Injection site reactions can be avoided by changing (rotating) the injection site at each injection. Local allergic reactions at the injection site (itching, hives) have also been reported.

- **Worsened scoliosis (curved spine caused by rapid growth)**
  If you have scoliosis, you will need to be checked often for an increase in the curve of the spine.

- **Benzyl alcohol toxicity**
  Benzyl alcohol is a preservative in Increlex. Benzyl alcohol can cause serious side effects, including death in infants who have received medicines that contain the benzyl

alcohol preservative (see Do not use Increlex).

The use of Increlex has not been studied in children under 2 years of age and is therefore not recommended.

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 Increlex:
- If you take insulin or other anti-diabetes medicines. A dose adjustment may be needed for these medicines.

How to take Increlex:
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Inject Increlex just under your skin shortly before or after a meal or snack. Do not inject your dose of Increlex if you cannot eat for any reason.

Inject Increlex just below the skin in your upper arm, upper leg (thigh), stomach area (abdomen), or buttocks. Never inject it into a vein or muscle. Change the injection site for each injection.

Before using Increlex, check to make sure the Increlex solution is clear and colourless.

Usual dose:
The typical dose is 0.04 to 0.12 mg/kg of patient weight administered twice a day. Your doctor will tell you how much Increlex you should inject based on your weight.

Overdose:
If more Increlex than recommended was injected, contact your doctor immediately.
Acute overdose could lead to hypoglycemia (low blood sugar). Treatment of acute overdose should be directed at reversing hypoglycemia. Sugar-containing fluids or food should be consumed.

Long-term overdose may result in enlargement of certain body parts (e.g., hands, feet, parts of the face) or excessive growth of the whole body. If you suspect long-term overdose, contact your doctor immediately.

If you think you have taken too much Increlex, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Do not make up the missed dose by giving two doses the next time. The next dose should be taken as usual, with a meal or snack.

What are possible side effects from using Increlex?
These are not all the possible side effects you may feel when taking Increlex. If you experience any side effects not listed here, contact your healthcare professional.

Very common side effects with Increlex are: low blood sugar (hypoglycemia), allergic reactions, injection site reactions, headache and snoring. Serious allergic reactions have also been reported with Increlex.

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	
VERY COMMON **Severe hypoglycemia**: signs of low blood sugar include dizziness, trouble concentrating, sweating, nausea, fast or irregular heartbeat.		X	X
Increased pressure in the brain (intracranial hypertension): headache, nausea, vomiting.		X	X
Injection site reactions: tissue at injection site increases in size, pain, redness, or bruising.		X	
Enlarged tonsils: snoring, difficulty breathing, sleep apnea (a condition where breathing stops briefly during sleep), or fluid in the middle-ear.		X	
A bone problem: limp or has hip or knee pain		X	
UNKNOWN **Tumour growths**: appearance of any new lumps or tumour growths anywhere on your body.		X	X
Allergic reaction: symptoms include trouble breathing, dizziness, pale, clammy skin or passing out, itching, hives.		X	X

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

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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:
Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vial in the carton in order to protect from light.
After first use, the vial may be stored for up to 30 days at 2°C to 8ºC.
Keep out of reach and sight of children.

If you want more information about Increlex:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.ipsen.ca, or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

Last Revised: August 10, 2021

Instructions for Use

Important:

- **Do not share your child's needles and syringes with another person.** Your child may give another person an infection or your child could get an infection from them.
- Inject Increlex exactly as your child's doctor or nurse has shown you.
- **Follow your doctor's instructions for the type of syringe and needle to use to prepare and inject your child's dose of Increlex**.
- Always use a new, unopened needle and syringe for each injection.
- Throw away used needles and syringes in accordance with local regulations.

Preparing the Dose:

1. Wash your hands before getting Increlex ready for your child's injection.
2. Check the liquid to make sure it is clear and colourless. **Do not** use if it is cloudy or if you see particles.
3. Check the expiration date printed on the label of the vial. **Do not** use Increlex if the

expiration date has passed.

4. If you are using a new vial, remove the protective cap. **Do not** remove the rubber top (see Figure 1).

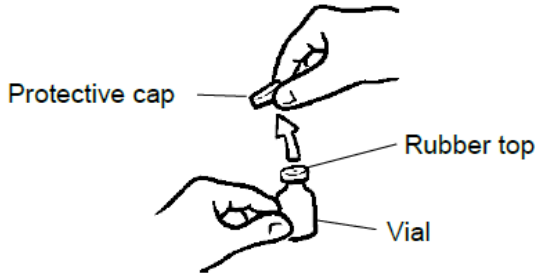


Figure 1: Remove the protective cap

5. Wipe the rubber top on the vial with an alcohol swab (see Figure 2).

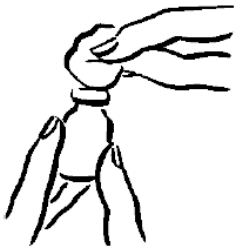


Figure 2: Wipe rubber top with alcohol swab

6. Before putting the needle into the vial, pull back on plunger to draw air into the syringe equal to the Increlex dose. Put the needle through the rubber top of the vial and push the plunger to inject air into the vial (see Figure 3).

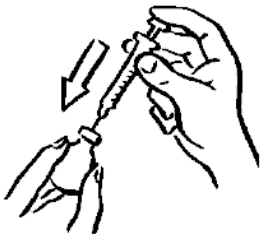


Figure 3: Inject air into vial

7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly (see Figure 4).

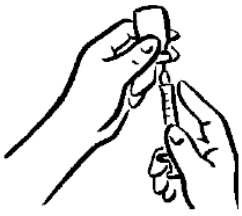


Figure 4: Prepare to withdraw liquid

8. Make sure the tip of the needle is in the liquid (see Figure 5). Pull the plunger to withdraw the correct dose into the syringe (see Figure 6).

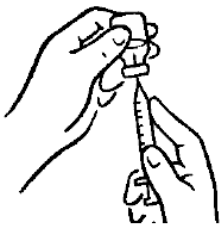


Figure 5: Tip in liquid

Figure 6: Withdraw correct dose

9. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the vial and syringe with needle straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw liquid back in until you have the correct dose (see Figure 7).

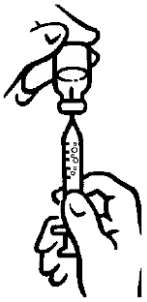


Figure 7: Remove air bubbles and refill syringe

10. Remove the needle from the vial. **Do not** let the needle touch anything. You are now ready to inject (see Figure 8).

Figure 8: Ready to inject

Injecting the Dose:

Inject Increlex exactly as your child's doctor or nurse has shown you.

Do not give the Increlex injection if your child is unable to eat within 20 minutes before or after the injection.

1. Choose an injection site – upper arm, upper leg (thigh), buttocks, or stomach area (abdomen) (see Figure 9). The injection site should be changed (rotated) for each injection.

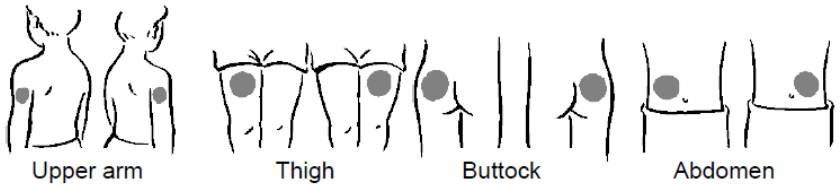


Figure 9: Injection site

2. Use alcohol to clean the skin where you are going to inject your child. The injection site should be dry before you inject.

   Do not fan or blow on the cleaned skin.

   Do not touch the injection site again before giving the injection.

3. Lightly pinch the skin. Insert the needle into the pinched skin as instructed by your child's doctor or nurse (see Figure 10). Release the pinched skin.


Figure 10: Lightly pinch the skin and inject as instructed

4. Slowly push the plunger of the syringe all the way in to make sure you have injected all of the liquid. Pull the needle straight out and gently press on the injection site with gauze or a cotton ball for a few seconds. **Do not** rub the injection site (see Figure 11).

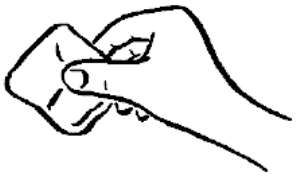


Figure11: Press (**do not** rub) with gauze or cotton ball