▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
INCRELEX®
mecasermin 10 mg/mL solution for injection

1 NAME OF THE MEDICINE

mecasermin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10 mg of mecasermin*.

Each vial of 4 mL contains 40 mg of mecasermin*.

*Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1(IGF 1) produced in *Escherichia coli*.

Excipient with known effect:

One mL contains 9 mg of benzyl alcohol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor 1 deficiency (Primary IGFD).

Severe Primary IGFD is defined by:

- height standard deviation score ≤ –3.0 and
- Baseline height velocity less than the 25th percentile for bone age, based on two measurements over 12 months 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.

IGF-1 and GH levels must be performed using validated assays with paediatric normal ranges.

4.2 DOSE AND METHOD OF ADMINISTRATION

INCRELEX is supplied as a multi-dose solution. Each vial is for use in one patient only.

Treatment with mecasermin should be under the supervision of a paediatric endocrinologist.

There should be documented confirmation of the diagnosis of severe IGF-1 deficiency at initiation of treatment, in line with guidance in the prescribing information (see section 4.1 THERAPEUTIC INDICATIONS). Ideally this will also include confirmation of mutation in the growth hormone/IGF signalling pathway consistent with severe IGF-1 deficiency.

The dose should be individualised for each patient. The recommended starting dose of mecasermin is 0.04 mg/kg of body weight twice daily by subcutaneous injection. If no significant adverse reactions occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. In the clinical trials, optimal growth response was seen with doses between 0.08 mg/kg and 0.12 mg/kg twice daily. Lower doses were less effective. Higher doses were more often associated with hypoglycaemia. Doses greater than 0.12 mg/kg twice daily should not be exceeded as this may increase the risk of neoplasia (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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.

Treatment should continue until bone age demonstrates fusion of epiphysis.

Paediatric population

The safety and efficacy of mecasermin in children below the age of two have not been established (see section 5.1 PHARMACODYNAMIC PROPERTIES). No data are available.

Therefore, the product is not recommended in children below the age of two.

Special Populations

Patients with renal impairment

There are limited data concerning the pharmacokinetics of mecasermin in children with renal impairment in this specific population of severe primary IGFD patients. It is recommended that the dose be individualised for each patient as described above.

Patients with hepatic impairment

There are limited data concerning the pharmacokinetics of mecasermin in children with hepatic impairment in this specific population of severe primary IGFD patients. It is recommended that the dose be individualised for each patient as described above.

Method of administration

INCRELEX should be administered by subcutaneous injection shortly before or after a meal or snack. If hypoglycaemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat, for any reason, this dose should be withheld. The dose of mecasermin should never be increased to make up for one or more omitted doses.

Injection sites should be rotated to a different site with each injection. INCRELEX should not be administered intravenously.

Precaution to be taken before manipulating or administering the medicinal product

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.

INCRELEX should be administered using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

INCRELEX is contraindicated in children and adolescents with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia.

Therapy should be discontinued if evidence of neoplasia develops.

As INCRELEX contains benzyl alcohol, it must not be given to premature babies or neonates.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mecasermin is not a substitute for GH treatment.

Mecasermin should not be used for growth promotion in patients with closed epiphyses.

Benign and malignant neoplasms

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 tumours.

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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The increased risk of neoplasia may be higher in patients who receive INCRELEX for unapproved uses or at higher than recommended doses. 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. If benign or malignant neoplasia develops, INCRELEX treatment should be discontinued definitely and appropriate expert medical care sought.

It is recommended that patients have a skin check at baseline and regularly during treatment for the documentation of any naevi.

Hypoglycaemia

Mecasermin may have insulin-like hypoglycaemic effects. It should be administered shortly before or during a meal or snack. Special attention should be paid to young children, children with a history of hypoglycaemia and children with inconsistent food intake. Blood glucose monitoring is recommended on initiation of treatment, during dose titration, periods of reduced oral intake or if the child is unwell. Patients should avoid engaging in any high-risk activities within 2-3 hours after dosing, particularly at the initiation of mecasermin treatment, until a well-tolerated dose of INCRELEX has been established. If a person with severe hypoglycaemia is unconscious or otherwise unable to ingest food normally, an injection of glucagon may be required. Persons with a history of severe hypoglycaemia should have glucagon available. At the time of initial prescription, physicians should educate parents on the signs, symptoms and treatment of hypoglycaemia, including injection of glucagon.

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

Other identified precautions

Echocardiogram is recommended before initiation of mecasermin treatment in all patients. Patients who terminate treatment should also have an echocardiogram. Patients with abnormal echocardiogram findings or cardiovascular symptoms should be followed regularly with echocardiogram procedures.

Lymphoid tissue (e.g. tonsillar) hypertrophy associated with complications, such as snoring, sleep apnoea, and chronic middle-ear effusions have been reported with the use of this medicinal product. Patients should have examinations periodically and at the occurrence of clinical symptoms to rule out such potential complications or to initiate appropriate treatment.

Intracranial hypertension (IH) with papilloedema, visual changes, headache, nausea and/or vomiting has been reported in patients treated with mecasermin, 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 mecasermin therapy and at the occurrence of clinical symptoms.

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 mecasermin treatment. Any patient with the onset of a limp or complaint of hip or knee pain should be evaluated.

In post-marketing experience in patients treated with INCRELEX, cases of hypersensitivity, urticaria, pruritus and erythema have been reported. These have been observed both as being systemic and/or local to the injection site. A small number of cases indicative of anaphylaxis requiring hospitalisation have been reported. 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.

Treatment should be reconsidered if, after one year, patients remain non-responsive.

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. Contact the sponsor for details on the antibody testing process (see Section 8 SPONSOR).

Benzyl alcohol

INCRELEX contains 9 mg/mL benzyl alcohol as a preservative

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

The risk inherent to benzyl alcohol is due to its accumulation. Elimination of benzyl alcohol is highly variable as both the age (immaturity) and ethnic polymorphism of alcohol dehydrogenase may lead to accumulation of benzyl alcohol and thus toxicity.

Use in the elderly

No data available.

Paediatric use

The product is for use in children and adolescents from 2 to 18 years only.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Doses of insulin and/or other hypoglycaemic medicinal products may need to be reduced (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Mecasermin has no effects on fertility in male and female rats at intravenous doses up to 4 mg/kg/day (estimated to yield up to 6 time in males and 3 times in females the clinical exposure with the [MRHD] based on AUC).

Use in pregnancy (Category B3)

There are no adequate data for the use of mecasermin in pregnant women.

Embryofetal lethality, but no malformations, occurred in rabbits given mecasermin intravenously at 2 mg/kg/day during the period of organogenesis. No adverse effects on embryofetal development were observed in rabbits at 0.5 mg/kg/day IV, or in rats at IV doses up to 16 mg/kg/day. The doses shown to be without adverse effect on embryofetal development in animals are associated with only low or modest multiples of the plasma AUC in patients at the MRHD.

This medicinal product should not be used during pregnancy unless clearly necessary.

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

Use in lactation.

Endogenous IGF-1 is detected in human milk. Breast-feeding while taking INCRELEX is not recommended, because there is insufficient information on the extent of excretion of mecasermin in human milk and the risk posed to the breastfed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

INCRELEX may have a major influence on the ability to drive or use machines in case of a hypoglycaemic episode. Hypoglycaemia is a very common adverse reaction.

Other adverse effects of INCRELEX include dizziness and convulsions which could also affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of safety profile

Adverse reaction data was taken from a total of 413 clinical trial patients with severe Primary IGFD. Data was also collected from post-marketing sources.

The most frequently reported adverse reactions from the clinical trials were headache (44%), hypoglycaemia (28%), vomiting (26%), injection site hypertrophy (17%), and otitis media (17%).

Intracranial hypertension/increased intracranial pressure occurred in 4 (0.96%) of patients from the clinical trials and occurred in 7 – 9 year old treatment naïve subjects.

During clinical trials in other indications totalling approximately 300 patients, reports of local and/or systemic hypersensitivity were received for 8% of patients. There were also reports of systemic hypersensitivity from post-marketing use, of which some cases were indicative of anaphylaxis. Post-marketing reports of local allergic reactions were also received.

Some patients may develop antibodies to mecasermin. No attenuation of growth was observed as a consequence of the development of antibodies.

Tabulated list of adverse reactions

Table 1 contains very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000, < 1/100) adverse reactions which occurred in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Other 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 (not known).

Table 1: Adverse reactions

Figure: 1. System Organ Class	**Reactions observed in the clinical trials**	**Reactions observed from the post-marketing environment**
Blood and lymphatic system disorders	Common: Thymus hypertrophy	

Immune system disorders		Not known: Systemic hypersensitivity (anaphylaxis, generalized urticaria, angioedema, dyspnoea), local allergic reactions at the injection site (pruritus, urticaria)
Metabolism and nutrition disorders	Very common: Hypoglycaemia Common: Hypoglycaemic seizure, hyperglycaemia	
Psychiatric disorders	Uncommon: Depression, nervousness	
Nervous system disorders	Very common: Headache Common: Convulsions, dizziness, tremor Uncommon: Benign intracranial hypertension	
Eye disorders	Common: Papilloedema	
Ear and labyrinth disorders	Very common: Otitis media Common: Hypoacusis, ear pain, middle ear effusion	
Cardiac disorders	Common: Cardiac murmur, tachycardia Uncommon: Cardiomegaly, ventricular hypertrophy, mitral valve incompetence, tricuspid valve incompetence	
Respiratory, thoracic and mediastinal disorders	Common: Sleep apnoea syndrome, adenoidal hypertrophy, tonsillar hypertrophy, snoring	

Gastrointestinal disorders	Very common: Vomiting, upper abdominal pain Common: Abdominal pain	
Skin and subcutaneous tissue disorders	Common: Skin hypertrophy, abnormal hair texture	Not known: Alopecia
Musculoskeletal and connective tissue disorders	Very common: Arthralgia, pain in extremity Common: Scoliosis, myalgia	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common: Melanocytic naevus	Not known: Benign and malignant neoplasms
Reproductive system and breast disorders	Common: Gynaecomastia	
General disorders and administration site conditions	Very common: Injection site hypertrophy, injection site bruising Common: Injection site pain, injection site reaction, injection site haematoma, injection site erythema, injection site induration, injection site haemorrhage, injection site irritation Uncommon: Injection site rash, injection site swelling, lipohypertrophy	
Investigations	Uncommon: Increased weight	
Surgical and medical procedures	Common: Ear tube insertion	

Description of selected adverse reactions

Neoplasms

There have been post-marketing reports of 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.3 CONTRAINDICATIONS).

Systemic/local hypersensitivity

Clinical Trials
During clinical trials in other indications (totalling approximately 300 patients) 8% of patients reported a local and/or systemic hypersensitivity reactions. All cases were mild or moderate in severity and none was serious.

Post-marketing reports
Systemic hypersensitivity included symptoms such as anaphylaxis, generalized urticaria, angioedema and dyspnoea. The symptoms in the cases indicative of anaphylaxis included hives, angioedema and dyspnoea. Some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients. There were also reports of local allergic reactions at the injection site. Typically, these were pruritus and urticaria.

Hypoglycaemia

Of the 115 (28%) subjects who experienced one or more episode of hypoglycaemia, 6 subjects experienced a hypoglycaemic seizure on one or more occasion. Symptomatic hypoglycaemia was generally avoided when a meal or snack was consumed either shortly before or after the administration of INCRELEX.

Injection site hypertrophy

This reaction occurred in 71 (17%) subjects from the clinical trials and was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved.

Tonsillar hypertrophy

This was noted in 38 (9%) subjects, particularly in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years.

Snoring

This occurred generally in the first year of treatment and was reported in 30 subjects (7%).

Intracranial hypertension/increased intracranial pressure

This occurred in 4 subjects (0.96%); in two subjects INCRELEX was discontinued and not restarted; in two subjects the event did not recur after restarting INCRELEX at a reduced dose. All 4 subjects recovered from the event without sequelae.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Acute overdose could lead to hypoglycaemia. 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.

Treatment of acute overdose of mecasermin should be directed at alleviating any hypoglycaemic effects. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous glucose or parenteral glucagon may be required to reverse the hypoglycaemic effects.

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 section 4.2 DOSE AND METHOD OF ADMINISTRATION)

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists.

ATC code: H01AC03

Mechanism of action

Insulin-like growth factor-1 (IGF-1) is the principal hormonal mediator of 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 signalling which stimulates multiple processes leading to 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.

Pharmacodynamic effects

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

Tissue Growth

Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by GH and IGF-1.

Organ growth: treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activity that leads to an increased number of cells in the body.

Carbohydrate Metabolism

IGF-1 suppresses hepatic glucose production, stimulates peripheral glucose utilization, and can reduce blood glucose and cause hypoglycaemia.

IGF-1 has inhibitory effects on insulin secretion.

Bone/Mineral Metabolism

Circulating IGF-1 plays an important role in the acquisition and maintenance of bone mass. IGF-1 increases bone density.

Clinical trials

Five clinical studies (4 open-label and 1 double-blind, placebo-controlled) were conducted with INCRELEX. Subcutaneous doses of mecasermin, generally ranging from 0.06 to 0.12 mg/kg given twice daily (BID), were administered to 92 paediatric subjects with severe Primary IGFD. Patients were enrolled in the studies on the basis of extreme short stature, slow growth rates, low IGF-1 serum concentrations, and normal GH secretion. Eighty-three (83) out of 92 patients were naïve to INCRELEX at baseline and 81 completed at least one year of INCRELEX treatment. Baseline characteristics for the 81 patients evaluated in the primary and secondary efficacy analyses from the combined studies were (mean ± SD): chronological age (years): 6.8 ± 3.8; age range (years): 1.7 to 17.5; height (cm): 84.1 ± 15.8; height standard deviation score (SDS): -6.9 ± 1.8; height velocity (cm/yr): 2.6 ± 1.7; height velocity SDS: -3.4 ± 1.6; IGF-1 (ng/ml): 24.5 ± 27.9; IGF-1 SDS: -4.2 ± 2.0; and bone age (years): 3.8 ± 2.8. Of these, 72 (89%) had Laron syndrome-like phenotype; 7 (9%) had GH gene deletion, 1 (1%) had neutralizing antibodies to GH and 1 (1%) had isolated genetic GH deficiency. Forty-six (57%) of the subjects were male; 66 (81%) were Caucasian. Seventy-four (91%) of the subjects were prepubertal at baseline.

Annual results for height velocity, height velocity SDS, and height SDS until year 8 are shown in Table 2. Pre-treatment height velocity data were available for 75 subjects. The height velocities at a given year of treatment were compared by paired t-tests to the pre-treatment height velocities of the same subjects completing that treatment year. The height velocities for years 2 through 8 remained statistically greater than baseline. For the 21 treatment naïve subjects with near-adult height, the mean (± SD) of the difference between

observed increase in height versus that expected from Laron was approximately 13 cm (± 8 cm) after an average of 11 years of treatment.

Table 2: Annual Height Results by Number of Years Treated with INCRELEX

	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 (1.7)	8.0 (2.3)	5.9 (1.7)	5.5 (1.8)	5.2 (1.5)	4.9 (1.5)	4.8 (1.4)	4.3 (1.5)	4.4 (1.5)
Mean (SD) for change from pre-Tx		+5.4 (2.6)	+3.2 (2.6)	+2.8 (2.4)	+2.5 (2.5)	+2.1 (2.1)	+1.9 (2.1)	+1.4 (2.2)	+1.3 (2. 8)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0042	0.0486
Height Velocity SDS									
N	75	75	62	62	58	50	37	22	15
Mean (SD)	-3.4 (1.6)	1.7 (2.8)	-0.0 (1.7)	-0.1 (1.9)	-0.2 (1.9)	-0.3 (1.7)	-0.2 (1. 6)	-0. 5 (1.7)	-0.2 (1.6)
Mean (SD) for change from pre-Tx		+5.2 (2.9)	+3.4 (2.4)	+3.3 (2. 3)	+3.2 (2.1)	+3.2 (2.1)	+3.3 (2.0)	+3.0 (2.1)	+3.3 (2.7)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.0003
Height SDS									
N	81	81	67	66	64	57	41	26	19
Mean (SD)	-6.9 (1.8)	-6.1 (1.8)	-5.6 (1.7)	-5.3 (1.7)	-5.1 (1.7)	-5.0 (1.7)	-4.9 (1.6)	-4.9 (1.7)	-5.1 (1.7)
Mean (SD) for change from pre-Tx		+0.8 (0.6)	+1.2 (0.9)	+1.4 (1.1)	+1.6 (1.2)	+1. 7 (1.3)	+1. 8 (1.1)	+1. 7 (1.0)	+1.7 (1.0)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001

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

[1] P-values for comparison versus pre-Tx values were computed using paired t-tests.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absolute subcutaneous bioavailability of mecasermin in severe Primary IGFD subjects has not been determined. The bioavailability of mecasermin after subcutaneous administration in healthy subjects has been reported to be approximately 100%.

Distribution

In blood, IGF-1 is bound to six IGF binding proteins (IGFBPs), with ~80% bound as a complex with IGFBP-3 and an acid-labile subunit. IGFBP-3 is reduced in subjects with severe Primary IGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects. The total IGF-1 volume of distribution (mean ± SD) after subcutaneous administration of INCRELEX in 12 subjects with severe Primary IGFD is estimated to be 0.257 (± 0.073) L/kg at a mecasermin dose of 0.045 mg/kg, and is estimated to increase as the dose of mecasermin increases. Limited information is available on the concentration of unbound IGF-1 after the administration of INCRELEX.

Metabolism

Both the liver and the kidney have been shown to metabolise IGF-1.

Excretion

The mean terminal $t_{1/2}$ of total IGF-1 after single subcutaneous administration of 0.12 mg/kg in three paediatric subjects with severe Primary IGFD is estimated to be 5.8 hours. Clearance of total IGF-1 is inversely proportional to serum IGFBP-3 levels and total IGF-1 systemic clearance (CL/F) is estimated to be 0.04 L/hr/kg at 3 mg/l IGFBP-3 in 12 subjects.

Pharmacokinetics in special patient populations

Elderly

The pharmacokinetics of INCRELEX have not been studied in subjects greater than 65 years of age.

Paediatric

The pharmacokinetics of INCRELEX have not been studied in subjects younger than 12 years of age.

Gender

In adolescents with Primary IGFD and in healthy adults there were no apparent differences between males and females in the pharmacokinetics of INCRELEX.

Renal impairment

No studies have been conducted in children with renal impairment.

Hepatic impairment

No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of mecasermin.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mecasermin was not clastogenic in an in vitro chromosomal aberration assay (conducted in Chinese hamster lung fibroblasts) or an in vivo mouse bone marrow micronucleus test. As a polypeptide, mecasermin is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of mecasermin, administered subcutaneously, was examined in a 2-year study in rats. An increased incidence of adrenal phaeochromocytoma was observed in male rats at doses of 1 mg/kg/day and above (≥ 1 times the clinical exposure at the MRHD based on AUC) and female rats at all dose levels (≥0.25 ng/kg/day; ≥ 0.2 times the clinical exposure).

An increased incidence of keratoacanthoma in the skin was observed in male rats at doses of 4 mg/kg/day and above (≥ 3 times the clinical exposure). An increased incidence of mammary gland carcinoma in both male and female rats was observed in animals treated with 10 mg/kg/day (4-5 times the clinical exposure).

IGF 1 is a known mitogen. The carcinogenic risk posed by mecasermin treatment in patients is mitigated by the context of its use as replacement therapy to normalise IGF-1 levels.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol
Sodium chloride
Polysorbate 20
Glacial acetic acid
Sodium acetate trihydrate
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After opening

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.

For use in one patient only.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

For storage conditions after first opening of the medicinal product, see Section 6.3 SHELF LIFE.

6.5 NATURE AND CONTENTS OF CONTAINER

5 mL vial (type I clear glass) closed with a grey stopper (bromobutyl/isoprene polymer) and an aluminium seal with a plastic flip-off button (lacquered plastic).

Pack size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

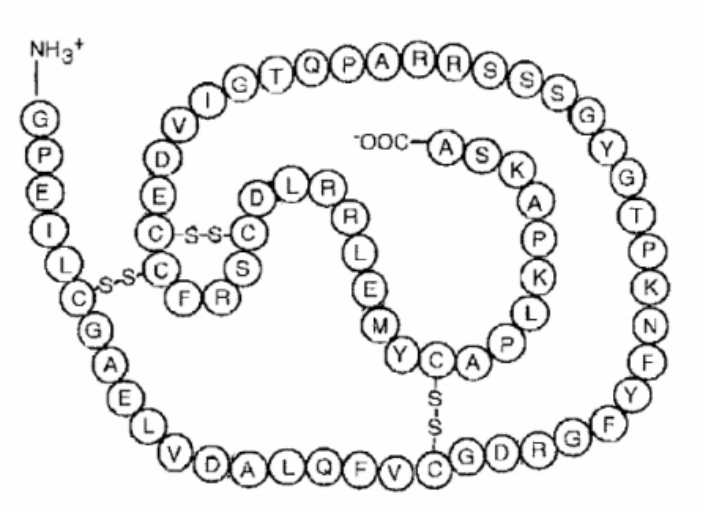
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Mecasermin human insulin-like growth factor-1 (rhIGF-1) is 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.

Primary Amino Acid Sequence of rhIGF-1



CAS number

68562-41-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

22 November 2019

10 DATE OF REVISION

N/A