Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Mecasermin

Proprietary Product Name: Increlex

Sponsor: Ipsen Pty Ltd

March 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALS	Acid labile subunit
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
BA	Benzyl alcohol
BD	Twice daily (Latin: *bis in die*)
CI	Confidence interval
CNS	Central nervous system
DLP	Data lock point
EMA	European Medicine Agency (EU)
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration (USA)
GH	Growth hormone
GHR	Growth hormone receptor
IGF-1	Insulin-like growth factor 1
IGF-BP3	Insulin-like growth factor binding protein 3
IGFD	Insulin-like growth factor 1 deficiency
IV	Intravenous
PIGFD	Primary insulin-like growth factor deficiency
PK	Pharmacokinetic(s)
rhIGF-1	Recombinant human insulin-like growth factor-1
RMP	Risk management plan
SC	Subcutaneous

Abbreviation	Meaning
SD	Standard deviation
SDS	Standard deviation score

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	19 November 2019
Date of entry onto ARTG:	22 November 2019
ARTG number:	308494
▼ *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Mecasermin
Product name:	Increlex
Sponsor's name and address:	Ipsen Pty Ltd 540 Springvale Road, Glen Waverley VIC 3150
Dose form:	Solution for injection
Strength:	10 mg/mL
Container:	Vial
Pack size:	1
Approved therapeutic use:	*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.*

Route of administration:	Subcutaneous (SC)
Dosage:	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 in the Product Information). 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 in Product Information). 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. For further information, refer to the Product Information.

Product background

This AusPAR describes the application by Ipsen Pty Ltd (the sponsor) to register mecasermin, a new biological entity, as Increlex for the following proposed 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*
> - *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, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.*

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

IGF-1 is a 70 amino acid peptide, which is 45 to 52% homologous to human insulin and 67% homologous to human IGF-2. In normal individuals, IGF-1 circulates as a complex

with an acid-labile subunit (ALS) and a binding protein, insulin-like growth factor protein 3 (IGFBP-3), which are dependent on growth hormone (GH). In target tissues, IGF-1 has one specific receptor, the insulin-like growth factor receptor 1 (IGFR1). IGF-1 is recognised to have anabolic, mitogenic and metabolic activities.

IGF-1 is the principal hormonal mediator of statural growth. Under normal circumstances, 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.

Severe primary insulin-like growth factor 1 deficiency (IGFD) includes patients with mutations in the GH receptor (GHR), post-GHR signalling pathway, and IGF 1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

Primary IGFD is a group of rare disorders of severe short stature. The most well known example would be Laron syndrome, which is due to defects in the GH receptor. Primary IGFD may also arise due to post-GHR signalling pathway defects, defects in the IGF-1 gene expression or IGF-1 production or antibodies to GH. These disorders are usually diagnosed clinically based on severe short stature.

The clinical expression in affected individuals varies. Affected individuals are close to normal size at birth but experience slow growth from early childhood resulting in very short statue. In Laron syndrome typically adult males reach a maximum height of 137 cm (range 116 to 142 cm) and females 122 cm (range 108 to 136 cm).[1] Affected individuals have short limbs, small hands and small feet. Other features may include reduced muscle strength and endurance, hypoglycaemia, delayed puberty, dental abnormalities, a facial appearance with protruding forehead and sunken bridge of the nose and blue sclera. Adults have a normal lifespan and whilst they tend to develop obesity, may have a reduced risk of type 2 diabetes mellitus and cancer.

Regulatory status

This is an application to register a new biological entity for Australian regulatory purposes.

The United States (US) Food and Drug Administration (FDA) approved Increlex on 30 August 2005 for the treatment of growth failure in children with severe primary IGFD, or those with GH gene deletion who have developed neutralising antibodies to GH.

Increlex was approved by the European Medicine Agency (EMA) on 3 August 2007 through the Centralised Procedure under exceptional circumstances (evaluated by a Rapporteur (Finland) and Co-Rapporteur (Hungary)) for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary IGFD. Increlex was launched in the EU on 31 October 2007.

In Japan, mecasermin (Somazon) has been available since 1995.

There are differences between US versus EU criteria for severe primary IGFD definition in relation to the circulating IGF-1 level (≤ -3.0 standard deviation (SD) score in the US versus < 2.5 percentile for age and gender in the EU). However, both require a height SD score ≤ -3.0, GH to be sufficient and additionally in the EU, for exclusion of secondary

[1] Laron, Z. Consequences of not treating children with Laron syndrome (primary growth hormone insensitivity*) J Pediatr Endocrinol Metab*. 2001; 14(Suppl 5): 1243–1248.

forms of IGFD. The FDA indication also includes patients with GH gene defects who have developed anti-GH antibodies.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-03520-1-5

Description	Date
Orphan designation	17 July 2018
Submission dossier accepted and first round evaluation commenced	3 October 2018
First round evaluation completed	1 March 2019
Sponsor provides responses on questions raised in first round evaluation	1 May 2019
Second round evaluation completed	17 July 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	28 August 2019
Sponsor's pre-Advisory Committee response	16 September 2019
Advisory Committee meeting	4 October 2019
Registration decision (Outcome)	19 November 2019
Completion of administrative activities and registration on the ARTG	22 November 2019
Number of working days from submission dossier acceptance to registration decision*	220

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Mecasermin is a single chain, non-glycosylated basic polypeptide produced by *Escherichia coli* fermentation.

The drug product is a sterile liquid formulation containing a preservative and is intended for multiple administrations by subcutaneous (SC) injection. It is supplied in glass vials with an elastomer stopper.

Each mL of Increlex contains 10 mg of mecasermin.

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

Increlex contains benzyl alcohol (BA) as a preservative.

The quality evaluator recommended approval on the condition that Good Manufacturing Practice (GMP) clearances were obtained from all relevant sites.

Nonclinical

- Dose-dependent increases in bone growth with SC mecasermin treatment were shown in two rat models of growth deficiency. The models used (hypophysectomised and mutant dwarf rats) show growth hormone and IGF-1 deficiency.
- Significant reductions in plasma glucose/hypoglycaemia following SC and/or intravenous (IV) administration of mecasermin were demonstrated in secondary pharmacodynamic studies in rats, rabbits and monkeys. This is consistent with the insulin-like action of IGF-1 to stimulate glucose uptake in muscle. The observed hypoglycaemic effects in rats occurred at doses of mecasermin higher than that required for its growth-promoting activity. Dose-dependent increases in body weight and stimulation of immune function were also demonstrated in mecasermin-treated animals.
- Mecasermin had no notable effects on the central nervous system (CNS), cardiovascular or respiratory function in treated animals.
- Absorption of mecasermin following SC administration was rapid in rats and rabbits, and moderately fast in dogs, similar to humans. Peak and overall exposure were less than dose-proportional in the key laboratory animal species (rats and dogs) like in humans; this is seen to be related to saturation of plasma protein binding (involving multiple IGF-1 binding proteins) and faster clearance of unbound drug. Bioavailability by the SC route was moderate (approximately 50%) in rats and rabbits (not examined in other species). A limited volume of distribution was evident in rats, like humans. Penetration of the blood-brain barrier was low.
- Mecasermin showed significant acute toxicity in rats and dogs. Deaths and clinical signs were related to (pharmacologically mediated) hypoglycaemia.
- Mecasermin was not clastogenic *in vitro* or *in vivo*.
- Repeat-dose toxicity studies by the clinical route (SC) of up to 6 months duration were conducted in rats and dogs, together with shorter studies (up to 13 weeks) by the IV

route in the two species. Rat and dogs are seen to be appropriate models for the investigation of mecasermin toxicity on pharmacodynamic and pharmacokinetic grounds, and with immunogenicity (to human protein) not or rarely encountered. Key treatment-related histopathological changes in the pivotal 6 month studies were limited to the thymus (increased cortex area in male rats) and adrenal (mild medullary hyperplasia with fibrosis in dogs). These and other findings in the studies are consistent with the known pharmacological effects of IGF-1 (for example, stimulation of thymopoiesis and adrenal cell proliferation; and hypoglycaemia, with stimulation of adrenal catecholamine production/secretion as a response).

- A 2 year SC carcinogenicity study in rats revealed treatment-related increases in adrenal phaeochromocytoma (both sexes), keratoacanthoma in skin (males) and mammary gland carcinoma (both sexes). The no observable adverse effect levels (NOAELs) for carcinogenicity are associated with exposure levels below that of patients. IGF-1 is a known mitogen.
- Key safety concerns identified from the nonclinical data set relate to hypoglycaemia, and potential carcinogenicity and embryofetal toxicity. It is noted however that 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.
- There were no objections on nonclinical grounds to the registration of mecasermin for the proposed indication.

Clinical

The clinical dossier contained information from a range of sources. These included the initial studies of mecasermin that supported registration in the FDA and EMA, as well as the follow-on studies. It also included the results of supporting studies of different indications, registry studies, post marketing safety assessments and literature references.

The information available in the dossier was limited in several aspects. This is not uncommon in the registration of medicines that have been available internationally for some time and for the treatment of a rare disease, however it does make the evaluation difficult.

Pharmacology

There were 8 pharmacokinetic (PK) studies including studies in healthy subjects and those with IGF-1 deficiency.

There were 2 bioequivalence studies demonstrating similar PK profiles of the IGF-1 produced from changes in the manufacturing processes.

Bioavailability is affected by binding-to-binding proteins and body size. Patients with severe IGF-1 deficiency have lower levels of IGF-BP3 thus higher clearance of IGF-1 and need twice daily dosing. Patients with adequate levels of IGF binding proteins and high baseline IGF-1 require lower doses and may respond to daily administration.

Efficacy

Study 11419

The main efficacy study was Study 11419. This was a long-term study of the use of recombinant human insulin-like growth factor-1 (rhIGF-1) in the treatment of children with short statue due to severe primary IGF-1 deficiency. It included patients treated in previous sponsor initiated trials, subjects who had previously received mecasermin from other sources, and treatment naïve children.

The inclusion criteria were as follows:

- growth failure associated with GH receptor defects, GH gene deletion defects and anti-GH antibodies;
- height SD score <-2.0 for age and gender;
- IGF-1 SD score <-2 for age and gender;
- growth rate <50 percentile for age and gender for >6 months prior to study start;
- open epiphyses;
- random or stimulated GH >10 ng/mL;
- failure to increase IGF-1 by 50 ng/mL in response to exogenous GH during an IGF-1 generation test (growth hormone insensitivity syndrome (GHIS) and Laron syndrome); or
- GH antibodies to exogenous GH with a binding capacity of > 10 µg/mL (GHIS and GH gene deletion).

This was an open labelled uncontrolled study. Patients received a range of doses, from 60 to 120 µg/kg. There were also 21 subjects who received leuprolide.[2]

Primary efficacy endpoints were height velocity and final adult height (near final adult height was defined as a bone age of 14 for girls and 16 for boys).

Secondary endpoints were height SD score and height velocity SD score.

The sample size was determined from the number of available subjects; 91 subjects were enrolled in Study 1419. Of these 26 completed the study; 2 were considered to have reached final adult height; and 24 met the criteria for near adult height.

At Baseline, 72 patients had a diagnosis Laron syndrome. One subject had isolated genetic GH deficiency. Three of the seven subjects with GH gene deletion had anti-GH antibodies. The subjects with severe primary IGFD were severely short with a mean estimated baseline height SD score of -6.9 (range: -12.1 to -2.8) and a mean estimated baseline IGF-1 SD score of -3.9 (range: -9.5 to -0.6). The mean pre-treatment height velocity was 2.6 cm/year. The average chronological age of the subjects at Baseline was 6.8 years, whereas their average bone age (3.8 years) was much delayed. Seventy-four of the 81 subjects (91%) were reported to be pre-pubertal (pubertal stage 1) at Baseline.

Table 2: Mean height velocity in treatment naïve children in Study 1419

	n	Mean±SD	p-value
Pretreatment	75	2.6±1.7	-
Year 1	75	8.0±2.3	<0.0001
Year 2	63	5.9±1.7	<0.0001
Year 3	62	5.5±1.8	<0.0001
Year 4	60	5.2±1.5	<0.0001
Year 5	53	4.9±1.5	<0.0001
Year 6	39	4.8±1.4	<0.0001
Year 7	25	4.3±1.5	0.0042
Year 8	19	4.4±1.5	0.0486
Year 9	14	4.4±1.7	0.2061
Year 10	13	4.5±2.0	0.2613
Year 11	12	4.1±2.0	0.4879
Year 12	10	3.9±2.0	0.9301
Year 13	9	3.3±1.7	0.7287
Year 14[a]	6	2.3±1.6	0.1372

n = number of subjects; SD = standard deviation

Source: Study 1419 CSR, Table 16.2.9.2 (Module 5.3.5.1.2)

a Data for Year 15 to Year 19 not presented as subject numbers were very low (≤4 subjects)

[2] Leuprorelin is a gonadotropin-releasing hormone (GnRH) analogue acting as an agonist at pituitary GnRH receptors.

As can be seen in Table 2, treatment with IGF-1 resulted in statistically significantly improved growth velocity for 8 years after treatment. After 8 years, the number of patients continuing was low; the reported growth velocity remained above Baseline but was not statistically significant.

There were 7 patients with a height velocity of < 5 cm/year after the first year of treatment. Most of these continued mecasermin but had a very poor growth outcome.

There was a significant dose effect. There was a small 0.9 year increase in chronological age for increase in bone age with treatment.

Twenty-one patients received treatment with leuprolide to delay puberty. The response to leuprolide was small. Of the 21 patients treated, the improvement in height SD ranged from -1.1 to 2.2. Only 3 subjects had a > 1 SD improvement in height SD score.

Nineteen treatment-naïve subjects attained near-adult height. Two other treatment-naïve subjects were considered by the investigators to have completed the intended course of treatment to near-adult height. The mean ± SD of the difference between the observed increase in height versus that expected from Laron syndrome was approximately 13 ± 8 cm after an average of 11 years of treatment.

Study MS301

This was a Phase III, randomised, open label, observational, multicentre parallel dose comparison trial in the US. Inclusion criteria were similar to Study 1419 except patients did not need to have a diagnosis of a GH receptor defects, GH gene defects or anti –GH antibodies.

Patients were initially randomised to receive 40 or 80 µg/kg mecasermin twice a day or placebo. During the first year of the study, it became apparent that patients assigned to the 40 µg/kg arm failed to raise the IGF-1 level into the desired range. Remaining patients had their dose increased to 120 µg/kg and those not yet treated were commenced on a dose of 120 µg/kg.

First year mean (± SD) height velocity was 5.2 (± 1.0), 6.9 (± 1.0) and 7.7 (± 1.5) cm/year in the untreated control, 80 and 120 µg/kg twice a day mecasermin groups, respectively. Height velocity during the first year was statistically significantly greater with both doses of mecasermin (80 and 120 µg/kg twice a day) than with the untreated control, with least square (LS) mean differences (95% confidence interval (CI)) versus untreated control of 1.79 cm/year (1.19, 2.39) and 2.58 cm/year (1.99, 3.16), respectively ($p < 0.0001$ for both comparisons).

Study 306

This was an extension of Study 301, with a planned duration of 5 years. Patients in the initial control group were randomised to receive 80 or 120 µg/kg twice a day; patients in the initial 80 µg/kg group had the dose increased to 120 µg/kg. During the study, there was a protocol amendment and patients had the dose increased to 160 µg/kg daily then 200 µg/kg and 240 µg/kg daily. The study was subsequently suspended due to a high rate of hypoglycaemia at doses above 200 µg/kg daily. Efficacy was analysed only in those who received 120 µg/kg twice a day. In the modified intention-to-treat (MITT) population, mean ± SD height velocity increased from pre-treatment (5.0 ± 2.3 cm/year) to 7.7 ± 1.5, 6.1 ± 1.4 and 5.9 ± 1.1 cm/year in Year 1, 2 and 3, respectively.

Study MS308

This open labelled study evaluated the effect of mecasermin on growth in pre-pubertal patients with IGF-1 deficiency. Inclusion criteria included height standard deviation score (SDS) < -2 for age and sex, IGF-1 SDS) < -2, chronological age > 3 years, chronological age or bone age < 12 in boys and < 11 years in girls, GH sufficiency. Patients received an initial dose of 60 µg/kg, the dose was titrated to achieve a serum IGF-1 level of +2 SD. Forty-five

children were enrolled, 43 subjects completed 34 weeks and 30 subjects completed 86 weeks. The growth response observed was less than other studies, height velocity increase by 1.3 ± 3.5 cm in the first year.

European Union registry

This registry was established in December 2008, primarily to assess safety. The date of the data cut off for the dossier was 10 May 2017.

Some 246 subjects were registered in the study; 63 had completed treatment (until final adult height) and 139 subjects discontinued treatment. Of those that had discontinued, 25 had reported that treatment was ineffective. At the time of the first intake, the mean age was 9.7 years, mean height velocity 4.75 cm/year. After one year of treatment, the mean height velocity was 6.84 cm/year and mean height SDS -3.4 ± 1.34. Twenty-five (25) subjects in treatment-naïve pre-pubertal subgroup reported a final adult. The mean final adult height was 159.8 ± 19.2 cm in boys (-2.3 ± 1.7 in terms of height SDS) and 150.2 ± 5.6 cm in girls (-2.3 ± 0.8 in terms of height SDS).

Safety

The information about safety comes from the clinical pharmacokinetics (PK), efficacy and safety studies, post market registries and reports from experience in the real world setting.

More than 1500 subjects have been exposed to mecasermin in clinical trials for diverse indications including primary IGFD. The populations in many of these studies are not representative of the proposed indication as they included patients with less severe short stature. Safety in other indications may not be representative of safety in the proposed indication for a number of reasons. Most of these studies were uncontrolled, thus it is not possible to know if the reported events were attributable to the medicine or other factors. In addition, replacement of IGF-1 to patients with a deficiency aims to achieve a physiological level of IGF-1, as opposed to treatment to achieve supra-physiological levels.

The mean duration of exposure in Study 1419 was 6.0 years with the majority taking 120 µg/kg twice a day. In the EU registry study, the mean duration of exposure was 3.5 years. In the US registry Study MS305, the mean duration was 2.1 years.

In Study 1419, the most common treatment emergent adverse events include hypoglycaemia, injection site hypertrophy, headache, snoring and pyrexia. A similar pattern of adverse events (AEs) but different reported prevalence were seen in the registry studies.

Hypoglycaemia

In Study 1419, approximately 47% of subjects experienced at least 1 episode of hypoglycaemia; of these 10 were severe. Hypoglycaemic was less common in the registry studies, it is unknown if this is due to less reporting or better advice being given to patients about the timing of administration.

The sponsor proposes the following advice in relation to the prevention of hypoglycaemia:

- mecasermin should be administered a short time before or after a meal or snack;
- if a patient is unable to eat, the dose should be withheld;
- therapy should be initiated at a low dose, and the patient monitored for hypoglycaemia. If no episodes have occurred for 7 days, the dose could be increased. Consider a dose reduction if hypoglycaemia occurs despite adequate oral intake; and
- parents should be educated about monitoring for hypoglycaemia.

Risk of malignancy

During the course of the evaluation, the sponsor provided some data in relation to a safety signal of increased risk of malignancy seen with mecasermin.

IGF-1 is known to be a mitogen. Patients with Laron syndrome have less cancer than the background population.

The sponsor reviewed their safety database and the medical literature. There had been approximately 36 cases of malignancy reported from the initial time of marketing until 2019. The number of patients exposed to mecasermin during that time is unknown. If data only from 2019 was considered when the exposure is known, the estimated rate of malignancy in patients exposed to mecasermin was around 4.5 times that in the background population.

It is important to note that most of the reported cases are rare forms of malignancy, some of the patients had other factors for malignancy, or were being treated with much higher doses that that recommended.

Benzyl alcohol

Benzoic acid and benzyl alcohol are excipients and mainly employed as solubilising agent and/or preservative in medicinal products. In pre-term and full-term neonates, concerns have been raised with the use of benzyl alcohol and benzoic acid. Benzyl alcohol administered IV has led to 'gasping syndrome' in several pre-term neonates with metabolic acidosis involving deterioration of the neurological state, cardiovascular failure and haematological anomalies. The majority of poisonings were fatal. This syndrome was associated with the accumulation of benzyl alcohol and its metabolite, benzoic acid. Benzyl alcohol must not be used in pre-term and full-term neonates.

The Delegate included a reference to an EMA report reviewing the labelling of benzoic acid products.[3] This report describes the cases reported in neonates and two older patients given very high doses:

- a 5 year old given 180 mg/kg benzyl alcohol over 36 hours; and
- a 53 year old man given 90 mg/kg as an infusion.

The EMA recommended some updates to the labelling, but still restrict use to children over 3 years.

In the clinical trials for mecasermin, patients over 2 years were enrolled. There were no reports of problems related to benzyl alcohol in these children.

The prescribing information for mecasermin recommends use in children over 3 years.[4]

Risk management plan

The sponsor has submitted European Union-risk management plan (EU-RMP) version 9.3 dated 23 August 2017, data lock point (DLP) 31 August 2016, and Australian specific Annex (ASA) version 1.0 dated 23 August 2018 in support of this application. The sponsor submitted a signal evaluation report dated 24 April 2019. Following the second round of evaluation, the sponsor submitted the EU-RMP (version 11.3, dated 22 October 2019, DLP 31 January 2018), with ASA (version 3.0, dated 8 November 2019).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 3.

[3] EMA, Committee for Human Medicinal Products (CHMP), Benzyl alcohol and benzoic acid group used as excipients, EMA/CHMP/272866/2013, 9 October 2017.
[4] European Union, Summary of Product Characteristics: Increlex (mecasermin).

Table 3: Summary of ongoing safety concerns[5]

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Neoplasia	✓1	✓2, 3, 4	✓	✓5
	Hypoglycaemia	✓	✓2	✓	✓5, 6, 7
	Lipohypertrophy	✓	✓2	✓	✓5, 6
	Tonsillar hypertrophy and associated AEs	✓	✓2	✓	✓5, 6
	Intracranial hypertension	✓	✓2	✓	✓5, 6
	Hypersensitivity	✓1	–	✓	✓5
	Scoliosis	✓	✓2	✓	✓5, 6
	Cardiomegaly	✓	✓2	✓	✓5
Important potential risks	Immunogenicity (potential reduced effect)	✓	–	✓	✓5
	Slipped capital femoral epiphysis	✓	✓2	✓	✓5, 6
	Off-label use (for indication)	✓	–	–	–
Missing information	Children under 2 years of age	✓	–	✓	–
	Pregnancy and lactation	✓	–	✓	–
	Renal impairment	✓	–	✓	–
	Hepatic impairment	✓	–	✓	–
	Cardiac impairment	✓	–	✓	–

1: Specific adverse reaction follow-up questionnair[e] 2: Increlex registry (EU); 3: long-term safety follow-up; 4: biennial review of cases; 5:Physician information pack; 6: Patient information pack; 7: Dosing guide.

[5] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine pharmacovigilance includes specific adverse reaction follow-up questionnaires. Additional pharmacovigilance consists of three ongoing overseas studies. The sponsor has proposed a controlled access program in the signal evaluation report to address the risk of neoplasia that includes assessment and documentation of patients and risk factors for malignancy prior to and during treatment. The program also requires enrolment of patients in a registry to ensure and document the risk minimisation activities.

Risk-benefit analysis

Delegate's considerations

1. Quality

There were no major concerns about the quality of this medicine. However, registration cannot occur until there is GMP clearance at all sites.

2. Description of primary IGF-1 deficiency in the indication

The sponsor's description involves clinical criteria and is similar to the inclusion criteria in the clinical trials. However, it is more restrictive of height criteria (with a cut-off of -3 SDS) and does not specify the need for a genetic diagnosis or low levels of IGF-BP3.

The following is an abstract from the Endocrine Society of America guidelines on GH and IGF-1 treatment:[6]

> *'7. IGF-I Treatment of Patients with PIGFD*
>
> *7.1. We recommend the use of IGF-I therapy to increase height in patients with severe PIGFD. (Strong recommendation, ●●●●)*
>
> *7.2. Given the absence of a single "best" test that predicts responsiveness to GH treatment, we suggest basing the diagnosis of PIGFD/GH insensitivity syndrome (GHIS) on a combination of factors that fall into 4 stages: (Conditional recommendation, ●●●○)*
>
> *1. Screening: auxological parameters and low IGF-I concentration*
>
> *2. Causes of secondary IGF-I deficiency must be excluded, including under-nutrition, hepatic disease, and GHD.*
>
> *3. Circulating levels of GH-binding protein (GHBP): very low or undetectable levels suggest Laron syndrome/GHIS while normal levels are noninformative.*
>
> *4. IGF-I generation test and mutation analyses can be helpful, but have limitations.'*

In the Delegate's opinion, the indication proposed is appropriate. However, the Delegate would appreciate expert paediatric endocrine comments in relation to cut off values for height SDS and IGF-1.

The PI will need to specify the need for IGF-1 level to be assessed by a validated assay with a paediatric normal range.

3. Efficacy

The efficacy studies were sub optimal in design in that they were open labelled, had small numbers, and involved variable dosing regimens. Overall, they indicate an improvement in growth velocity; the greatest improvement was in the first year. The effect decreases after

[6] Grimberg A. et al. (2016). Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr* 2016; 86: 361–397

this. Of the patients who reached final height, the height SDS was greater than that at the start of treatment but remains well below normal. Not all patients respond. There were no clearly identifiable factors to predict poor response.

A number of factors may have contributed to variable response in patients, including low levels of IGF-BP3 in some patients, different diagnosis and thus pathophysiology of growth failure, different doses, nutritional factors, age, and other medical issues.

4. Dose

The dose recommended is consistent with that recommended in the EU and USA. In Japan, the recommended dose is 0.05 to 0.2 mg/kg SC once daily.

The data in support of the dosing regimen is limited. It appears that 0.04 to 0.06 mg/kg is the lowest effective dose, however some patients did not respond to this. Patients respond better to higher doses. Doses over 0.2 µg/kg are associated with hypoglycaemia.

The following is an excerpt from the Paediatric Endocrine Society Guidelines:[6]

> *'7.3. We recommend a trial of GH therapy before initiating IGF-I for patients with unexplained IGF-I deficiency. Patients with hormone signaling defects known to be unresponsive to GH treatment can start directly on IGF-I replacement; these include patients with very low or undetectable levels of GHBP and/or proven GH receptor (GHR) gene mutations known to be associated with Laron syndrome/GHIS, GH-neutralizing antibodies, STAT5b gene mutations, and IGF1 gene deletion or mutation. (Strong recommendation, ●●○○)*
>
> *7.4. We suggest an IGF-I dose of 80-120 µg/kg b.i.d. Similar short-term outcomes were seen with 80 and 120 µg, but published studies had limitations and there is no strong evidence supporting superiority of one dose over the other. (Conditional recommendation, ●●○○).'*

The sponsor has proposed a starting dose of 0.04 mg/kg to reduce the risk of hypoglycaemia, and a slow increase in dose as tolerated. This is acceptable; however, the Delegate would recommend the dosing section be amended to clarify that clinicians should aim for a target dose of at least 0.1 mg/kg for optimal response, as there was data to support this.

5. Safety

The safety of this product is similar to that GH.

The main concern is hypoglycaemia, patients who are young and/or with severe short stature or with poor eating behaviours will be most at risk. There is information in the PI and Consumer Medicine Information (CMI) recommending slow dose increase and administration of mecasermin prior to meals. The sponsor has not proposed routine blood glucose monitoring during dose titration. The Delegate is of the view that monitoring should be recommended in patients at risk.

6. Malignancy

Nonclinical and epidemiological data indicate that the IGF-1 is a mitogen. Thus, it is plausible that mecasermin may potentiate the risk of malignancy. However, in the safety update provided by the sponsor, most of the patients who developed a malignancy when using mecasermin were using it in ways not recommended by the PI.

In the Delegate's opinion, the risk of malignancy in the population in which use is proposed and at the doses recommended remains unknown.

The Delegate is of the opinion that this potential risk does not prevent the registration of mecasermin provided the information is provided in the PI and that there is ongoing pharmacovigilance for this potential risk.

7. Off label use

The TGA is not able to regulate off label use. However, the Delegate considers this worthy of discussion given the difficulties in the diagnosis of some cases of growth failure.

8. Funding and integration with the GH program

The sponsor is in the early stages of planning a Pharmaceutical Benefit Access Committee (PBAC) submission for mecasermin. It is not known if it will be part of the Section 100 Growth Hormone Program.[7] The sponsor will be consulting with the Department of Health, through the pre-submission route (at a date not currently set), to assess whether this would indeed be the appropriate place for a Pharmaceutical Benefits Scheme (PBS) listing.

Questions for the sponsor

Question 1

What is the outcome of the safety notification in Europe?

Sponsor's response

A Type II labelling variation was submitted to EMA 30 May 2019; the assessment procedure commenced on 22 July 2019.

Overall conclusion and impact on the benefit/risk balance from the assessment report dated 5 September 2019 states the following:

> *'[…] the proposed additional measures to ensure that the use of mecasermin is limited to approved indications only, and the approved posology is followed, are endorsed. In addition, raising awareness of this serious potential risk and extending the contraindication from pre-existing malignancies to conditions potentially increasing the risk of malignancy, is endorsed.*
>
> *In general, the proposed changes in the Product information are considered acceptable to achieve these goals. Some minor modifications in the SmPC, RMP and DHPC are proposed. The benefit-risk balance of Increlex, remains positive.'*

As the assessment procedure in Europe is not due to be completed prior to the due date for this pre-ACM response, Ipsen commits to providing the TGA Delegate with a further update for sharing with the Advisory Committee on Medicines (ACM).

Question 2

Please provide further details of the controlled access program and patient registry. Will these be implemented in Australia?

Sponsor's response

The sponsor has an ongoing Increlex EU registry that commenced in December 2008 covering 10 countries. The details of the EU registry are summarised in the dossier submitted to TGA.

The sponsor plans to set-up a similar Increlex patient registry for Australia. The Australian Increlex patient registry will be an observational, non-interventional prospective safety study. Its primary objective will be to collect long-term safety data for all patients who have been treated with Increlex in Australia, with special focus on, but not limited to its identified and potential risks. It is currently planned that this study will be part of a global

[7] The Australian Government provides Pharmaceutical Benefits Scheme (PBS) subsidised access for somatropin (recombinant growth hormone) to eligible paediatric and adult patients through the Growth Hormone Program established under section 100 of the National Health Act 1953.

Increlex registry, which will collect and analyse the worldwide safety data for Increlex. The registry will follow-up patients post Increlex administration from 2 to 5 years. Interim reports will be submitted to TGA at periods discussed and agreed upon with TGA. More details and synopsis of the protocol for the Australian Increlex patient registry will be submitted to TGA when available.

Question 3

What is the justification for a cut-off of 3 years for use of medicines with benzyl alcohol as an excipient?

Sponsor's response

Increlex is indicated for use in children from 2 to 18 years of age with severe primary IGFD. It has been used in clinical trials in children from 2 years without significant concern. It is contraindicated in premature babies or neonates as it contains benzyl alcohol. The text initially proposed in the draft Australian PI in Section *4.4 Special warnings and precautions for use - Benzyl alcohol,* Increlex with respect to a precaution for use in children under 3 years of age, was included to align with the same text in the Increlex EU Summary of Product Characteristics (SmPC) as per the 2003 EMA recommendation for all products containing benzyl alcohol. The sponsor has updated this text as proposed by TGA, to remove this age specification, in line with the new 2017 EMA recommendation.

Questions for paediatric endocrinologist

1. Please comment on the proposed indication
    a. Is height a SDS score of -3 SDS appropriate?
    b. Is the EU defined criteria of IGF-1 less than the 2.5th percentile for age and sex appropriate for Australia, or should US definition of -3 SD be used?
2. Please comment about how IGF-1 levels are analysed and reported in Australia. Do they report a percentile or SDS score?
3. Please comment on the dose recommendations. Should more information about dose escalation be provided?
4. Please comment on the need for monitoring of blood glucose levels.
5. Do you consider the cases of malignancy detected in the post market database of sufficient concern to prevent registration? Please comment on the adequacy of wording in the PI.
6. Please comment on the likelihood of clinicians using this medicine in patients with less severe forms of growth failure who do not respond to GH.

Questions for toxicology expert

1. Please comment on the labelling of benzyl alcohol as an excipient.

Summary of issues

- The proposed indication is severe primary IGF-1 deficiency. This is a clinical diagnosis; based on very short stature, low IGF-1, normal or high GH levels and exclusion of secondary causes. The clinical trial included patients with height SDS of less than -2; however, the proposed indication uses a height SDS -3. The EMA use an IGF-1 level of less than the 2.5th percentile, but FDA less than -3 SDS. The clinical trial included patients with GH gene defects and antibodies to GH. In the clinical trials, there was a

poor response to low doses of 40-60 µg/kg twice daily. The PI recommends this as a starting dose with up titration as tolerated.

- Hypoglycaemia can occur with IGF-1 deficiency, however is also exacerbated by treatment with IGF-1 due to the insulin like effects. The risk is mitigated by giving mecasermin with meals. The risk of hypoglycaemia is described in the PI with recommendations to prevent this. However, the sponsor has refused to recommend monitoring due to a perceived burden on patients.
- Cases of metabolic acidosis and death have occurred in neonates treated with high doses of benzyl alcohol. Neonates, particularly premature infants, are at higher risk of complications due to their smaller size and immature liver. The labelling of products containing benzyl alcohol recommends not administering products containing this excipient in children less than 3 years. The mecasermin clinical trials included patients over 2 years. Patients' growth responded better to mecasermin when this was given early.
- In a post market safety update, 36 cases of malignancy have been described. These have mainly occurred in patients treated in other indications and with higher doses. The number of patients exposed to mecasermin during this time is unknown; however, the increased risk may be 4 to 5 times that of the background population.

Request for ACM advice

1. Please comment on the proposed indication:
    a. Is height a SDS score of -3 SDS appropriate?
    b. Is the EU defined criteria of IGF-1 less than the 2.5th percentile for age and sex appropriate for Australia, or should the US definition of -3SD be used?
2. Please comment about how IGF-1 levels are analysed and reported in Australia. Do they report a percentile or SDS score?
3. Please comment on the dose recommendations: Should more information about dose escalation be provided?
4. Please comment on the need for monitoring of blood glucose levels.
5. Please comment on the labelling of benzyl alcohol as an excipient.
6. Do you consider the cases of malignancy detected in the post market database of sufficient concern to prevent registration? Please comment on the adequacy of wording in the PI.
7. Please comment on the likelihood of clinicians using this medicine in patients with less severe forms of growth failure who do not respond to GH.

Advisory Committee Considerations[8]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM considered this product to have an overall positive benefit-risk profile for the proposed indication:

> *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;*
> - *baseline height velocity less than the 25th centile for bone age, based on three measurements over 12 months;*
> - *basal IGF-1 levels below the 2.5th percentile for age and gender;*
> - *stimulated IFG-1 levels (via IGF Generation Test) below the 2.5th percentile for age and gender;*
> - *mutation in the growth hormone/IGF signalling pathway consistent with resultant severe IGF-1 deficiency;*
> - *GH sufficiency; and,*
> - *exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.*
>
> *Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signalling pathway, and IGF 1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. Please comment on the proposed indication:

a. Is height a SDS score of -3 SDS appropriate?

The ACM was of the view that this height score would appropriately capture children with true severe IGF deficiency/GH resistance and is consistent with international practice.

b. Is the EU defined criteria of IGF-1 less than the 2.5th percentile for age and sex appropriate for Australia, or should US definition of -3 SD be used?

[8] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM was of the view that the EU defined criteria for IGF-1 was appropriate, noting that this is in keeping with Australian pathology lab reporting practices.

2. ***Please comment about how IGF-1 levels are analysed and reported in Australia. Do they report a percentile or SDS?***

   The ACM advised that IGF-1 assays in Australia report normal ranges calibrated to Bidlingermaier et al.;[9] international standard with an upper of 97.5% and lower limit of 2.5%. The ACM noted that while these centiles can be converted to SDS, this is rarely done.

3. ***Please comment on the dose recommendations. Should more information about dose escalation be provided?***

   The ACM was of the view that the PI section on dose escalation, based on Chernausek et al.;[10] should be amended to say that:

   - 'If no significant adverse reactions occur at least one week, *especially evidence of hypoglycaemia,* the dose may be raised…'
   - 'In the clinical trials, *optimal* growth response was *seen with doses between 0.80 – 0.12mg/kg twice daily. Lower doses were less effective, while higher doses were more often associated with hypoglycaemia, and* have not been *formally* evaluated in children with severe primary IGFD.'

4. ***Please comment on the need for monitoring of blood glucose levels.***

   The ACM was of the view that blood glucose monitoring should be advised during the dose optimisation phase, as well as during periods of illness or inadequate nutritional intake. The ACM suggested that wording should be included to ensure that parents are trained in blood glucose analysis and that they have access to appropriate equipment to enable them to perform it.

5. ***Please comment on the labelling of benzyl alcohol as an excipient.***

   The ACM agreed with the Delegate that the risk posed by the use of benzyl alcohol as an excipient was overstated. The ACM noted that current warnings were in line with EU guidelines and considered that the need for this warning could be reviewed on a wide scale basis at a later stage, but for the moment considered it reasonable to retain the warning for this product, with a modification to allow for use from 2 years of age.

6. ***Do you consider the cases of malignancy detected in the post market data base of sufficient concern to prevent registration? Please comment on the adequacy of wording in the PI.***

   The ACM did not consider the cases of malignancy detected in post market data to be of sufficient concern as to prevent registration. However, the ACM was of the view that the PI should be amended to emphasise the importance of monitoring IGF-1 levels during treatment to ensure they remain within normal range, and to advise baseline and biannnual skin surveillance while on treatment.

7. ***Please comment on the likelihood of clinicians using this medicine in patients with less severe forms of growth failure who do not respond to GH.***

[9] Bidlingmaier, M. et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. *J Clin Endocrinol Metab*. 2014; 99(5): 1712-1721.
[10] Chernausek, S.D. et al. Comparative pharmacokinetics of rhIGF-I in children with growth disorders. *Horm Res*, 1997; 48(Suppl 2): 47.

The ACM advised that there is significant risk of inappropriate prescribing for patients who do not have a true primary IGFD, based on current experience in the US where this product is registered. The ACM proposed several amendments to the wording of the indication to further restrict the use of the product to those patients with a proven mutation in the GH/IGF axis, consistent with severe IGFD. The ACM also advised that the IGF generation test should be a requirement for treatment in order to demonstrate the presence of low IGF-1, and that a criterion for baseline height velocity below the 25th percentile should be added in order to be consistent with requirements for treatment with GH.

General advice

The ACM was of the view that the PI and CMI should be amended to more fully inform prescribers and patients of the post marketing surveillance information and risks relating to malignancy, and that appropriate prescriber education on this issue should be undertaken.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Increlex (mecasermin 10 mg/mL) solution for injection, indicated:

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.*

Specific conditions of registration applying to these goods

- Increlex (mecasermin) is to be included in the Black Triangle Scheme. The PI and CMI for Increlex must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Increlex mecasermin EU-RMP, version 11.3, dated 22 October 2019, (data lock point 31 January 2018), with Australian specific Annex, version 3.0, dated 8 November 2019, included with submission PM-2018-03520-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- For all injectable products, the PI must be included with the product as a package insert.
- The CMI must be included with the products as a package insert. The CMI should have a link to the full version of the PI on the TGA website.
- Batch release testing & compliance with Certified Product Details (CPD)
  - All batches of Increlex imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - Each batch of Increlex imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
  - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories Branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

    This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Attachment 1. Product Information

The PI for Increlex approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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