5.09 MECASERMIN, Solution for injection 40 mg in 4 mL vial, Increlex®, Ipsen Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 listing for mecasermin 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 (SPIGFD).

1.2 The submission requested listing in the Section 100 Highly Specialised Drugs Program, however also noted that "the Section 100 Growth Hormone program appears to be the most appropriate place for reimbursement…". The Pre-Sub-Committee Response (PSCR) stated that given the potential risks of diversion and the need to ensure the quality use of medicines through treatment with appropriately qualified individuals, the sponsor would welcome a listing of mecasermin in the Section 100 Growth Hormone program for this small group of patients.

1.3 Listing was requested on the basis of a cost-utility analysis versus no treatment.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Long-term treatment of growth failure in children and adolescents from 2 to 18 years (inclusive) with SPIGFD
Intervention	Mecasermin 40-120 µg/kg BID, subcutaneous injection administered until there is demonstration of bone age fusion of epiphysis
Comparator	No treatment
Outcomes	Primary outcome: • Height velocity Secondary outcomes: • Skeletal maturation • Safety
Clinical claim	In children and adolescents (2-18 years) with SPIGFD, mecasermin is superior in effectiveness compared with no treatment based on changes in height over time and near-adult height compared with untreated patients. Mecasermin is non-inferior in safety compared with no treatment based on overall AE and SAE rates

AE = adverse events; BID = twice daily; SAE = serious adverse events; SPIGFD = severe primary insulin-like growth factor 1 deficiency.
Source: Table 1-2, p17 and Section 2, p90 of the submission.

2 Background

Registration status

2.1 Mecasermin was Therapeutic Goods Administration (TGA) registered in November 2019 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). Orphan drug designation was granted on 17 July 2018 (Clinical Evaluation Report, p 12).

2.2 The TGA approved product information (PI) states that 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
- Growth hormone (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.

2.3 At the time of evaluation for Pharmaceutical Benefits Advisory Committee (PBAC) consideration, the Australian Public Assessment Report, PI, Public Summary, and Orphan Drug Designation Application were available.

The PSCR described the sponsor's determination that an Australian registry "is not viable, given the small number of patients, the voluntary nature for the participation (in other countries it is possible to make it mandatory) and high cost of establishing the registry through a Clinical Research Organisation". However the PSCR also refers to a "controlled access program", which has been implemented, and that the sponsor proposes is sufficient to manage the identified risk of neoplasias.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
MECASERMIN					
mecasermin solution for injection 40 mg in 4 mL vial, 1	4	4	5	S100 Private Hospitals & Community Access $[redacted] S100 Public Hospitals $[redacted]	Increlex

Category / Program: Section 100 (program to be determined)
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ Authority Required (In-writing only via post/HPOS upload)
Note: No increase in the maximum quantity or number of units may be authorised.
Note: No increase in the maximum number of repeats may be authorised.
Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Episodicity: *[blank]*
Severity: *Severe*
Condition: *growth failure with primary insulin-like growth factor-1 deficiency*
Indication: Severe growth failure with primary insulin-like growth factor-1 deficiency
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be caused by severe primary insulin-like growth factor-1 deficiency (IGFD), with IGFD deficiency for the purpose of PBS-subsidy defined as a basal IGF-1 level (measured any time prior to initiating treatment with this drug) below the 2.5th percentile adjusted for each of: (i) age, (ii) gender; state in this authority application the patient's basal IGF-1 level measured in ng/mL, including the measurement date in dd/mm/yy, plus the name of the pathology result provider
AND
Clinical criteria:
The condition must have resulted in the patient experiencing short stature, with short stature for the purpose of PBS-subsidy defined as the patient's height (measured any time prior to initiating treatment with this drug) being at least 3 standard deviations below the norm, adjusted for each of: (age), (ii) gender; state in this authority application the patient's height in centimetres, including the measurement date in dd/mm/yy
AND
Clinical criteria:
The condition must have resulted in the patient experiencing slow growth, with slow growth for the purpose of PBS-subsidy defined as a baseline height velocity (measured any time prior to initiating treatment with this drug) less than the 25th percentile for bone age, based on 2 measurements over 12 months; state in this authority application each of the 2 height velocity measurements in cm/year, including the 2 time points the measurements were observed in month/year.
AND
Clinical criteria:

The condition must not be caused by growth hormone deficiency – substantiate this by stating in this authority application the patient's measured (any time point) peak growth hormone level in ug/L, along with the pathology provider's stated lower range of 'normal'
AND
Clinical criteria:
The condition must not be caused by secondary causes of IGFD – prior to initiating treatment with this drug, the treating physician has at least excluded each of the following: (i) malnutrition, (ii) hypopituitarism, (iii) hypothyroidism, (iv) medication side-effects
Treatment criteria:
~~Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology.~~ *Must be treated by a specialist physician identifying as one of: (i) a paediatric endocrinologist,; the authority application form must be completed by the specified physician type; OR*
Must be treated by a paediatrician who has consulted the above mentioned specialist type, with the authority application form completed by this paediatrician.
Population criteria:
Patient must be aged from 2 years up until their 19th birthday
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescriber instructions: *Maximum quantity/amount of drug selection:* *At the time of the authority application, state the following:* *(i) the patient's weight in kg;* *(ii) the prescribed dose (between 0.04 to 0.12 mg/kg);* *(iii) the number of vials rounded to the nearest whole number, to provide sufficient drug quantity for 4 weeks treatment.*
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
The treatment must be in a patient in which height is either: (i) still increasing, (ii) reasonably expected to increase
AND
Clinical criteria:
The treatment must not be in a patient with known epiphyseal closure/growth plate fusion (i.e. the patient is known to have ceased growing)
AND
Clinical criteria:
The treatment must not be in a patient where their height has ceased to increase (i.e. plateaued) over the preceding 12 months relative to the date of this authority application
Treatment criteria:

~~Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology.~~ *Must be treated by a specialist physician identifying as one of: (i) a paediatric endocrinologist,; the authority application form must be completed by the specified physician type; OR*
Must be treated by a paediatrician who has consulted the above mentioned specialist type, with the authority application form completed by this paediatrician.
Population criteria:
Patient must be aged from 2 years up until their 19th birthday
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescriber instructions: *Maximum quantity/amount of drug selection:* *At the time of the authority application, state the following:* *(i) the patient's weight in kg;* *(ii) the prescribed dose (between 0.04 to 0.12 mg/kg administered twice daily);* *(iii) the number of vials rounded to the nearest whole number, to provide sufficient drug quantity for 4 weeks treatment.*
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*

3.2 The submission did not propose any special pricing arrangement.

3.3 There were some inconsistencies between the proposed Pharmaceutical Benefits Scheme (PBS) restrictions and the evidence presented in the submission. Study 1419 included patients with height standard deviation score (HSDS) <-2.0 (compared to -3.0 in the PBS restriction) and patients with growth failure associated with GH receptor defects or GH gene deletion defects and anti-GH antibodies (compared to no restriction associated with specific genetic mutations in the proposed restriction). Trial MS301 included patients with HSDS <-2.0 and excluded patients with a documented mutation of GH receptor (Laron syndrome) or GH gene deletion (compared to no restriction associated with specific genetic mutations in the proposed restriction). The EU-IGFD Registry included all registered participants, 36 of which were not severe.

3.4 The evaluation noted that definitions of "growth hormone sufficiency", "improvement in height velocities" and "demonstration of bone age fusion of epiphysis" are unclear. The PBAC considered a more precise definition of GH sufficiency and adequate response to treatment was required to minimise the risk of use outside circumstances considered cost-effective and continuation of treatment in the absence of clinical benefit. The PBAC considered that revised continuation criteria similar to those applying to growth hormone would assist in clearly outlining circumstances of cost-effective use. The PBAC agreed with the Secretariat suggestion that there should be

documented confirmation of the diagnosis of severe IGF-1 deficiency at treatment initiation, which may include confirmation of mutation in the growth hormone/IGF signalling pathway consistent with severe IGF-1 deficiency, in line with guidance in the PI.

3.5 The PBAC noted that a wide range of general health conditions are associated with a low or undetectable level of IGF1. In general, conditions such as GH deficiency or multisystem auto immune inflammatory disorders have low GH, but there are a number of stress related conditions where growth hormone levels are high in the presence of extremely low IGF1, most notably psychosocial growth failure (deprivation).

For more detail on PBAC's view, see Section 7 PBAC outcome.

4 Population and disease

4.1 Short stature is defined as a height more than two standard deviations below the mean for age, sex and pubertal stage of the reference population. Short stature can be caused by GH-insulin-like growth factor 1 (IGF-1) axis defects. SPIGFD in children and adolescents is associated with more severe growth defects than GH deficiency.

4.2 SPIGFD is defined by HSDS score ≤ –3.0; baseline height velocity less than the 25th percentile for bone age, based on two measurements over 12 months; basal IGF-1 levels below the 2.5th percentile for age and gender; GH sufficiency; and exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

4.3 SPIGFD can also have consequences other than impaired growth in the short-term, including acromicria including facial bones, small gonads and genitalia, defective and crowded teeth, sparse hair growth, obesity, retarded brain growth and skeletal maturation, delayed motor development and puberty, and narrow larynx. Long-term consequences besides short stature include marked progressive obesity, muscle underdevelopment, varying intellectual deficits (from retardation to normal), glucose intolerance and diabetes, and hypercholesterolaemia. The ESC highlighted that none of these consequences were considered in the economic model, especially long-term and it was unclear to what extent mecasermin treatment would lead to improvements in these other consequences of SPIGFD. However, the condition did not appear to affect lifespan and may be associated with a reduced risk of cancer.[1]

4.4 Children with short stature have worse quality of life (QoL) compared to children with normal height. Short stature may be a risk factor for psychosocial problems, generalised anxiety, depression, and suicide.

[1] Laron Z. Lessons from 50 years of study of Laron syndrome. Endocrine Practice. 2015 Dec 1;21(12):1395-402.

4.5 The orphan drug designation application to the TGA of mecasermin estimated between 134 and 1,274 patients. The submission estimated the number of eligible patients using data from the EU-IGFD Registry and sales data from five European countries to be far fewer, 15 patients by 2027.

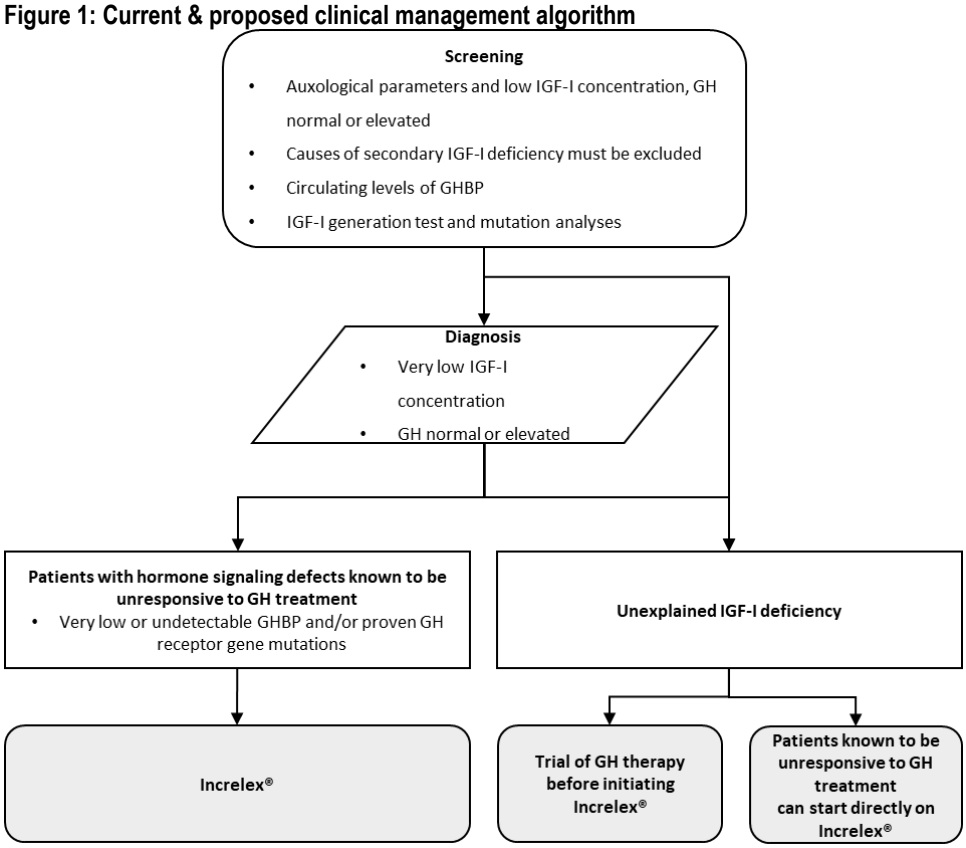
4.6 Mecasermin is the only therapy to date for the treatment of SPIGFD. Mecasermin is a recombinant DNA-derived human IGF-1 produced in Escherichia coli, which acts as replacement therapy for IGF-1 in patients with SPIGFD. As IGF-1 is the principal hormonal mediator of statural growth, and deficiency in IGF-1 results in short stature. As a result, mecasermin stimulates body growth in the same way as IGF-1.

4.7 Mecasermin has been described as an anabolic hormone usually abused among athletes to improve physical capacity and individuals seeking to enhance body aesthetics.[2] There is a potential risk of misuse of mecasermin outside its approved indications, similar to that of somatropin.

4.8 The submission presented a clinical management algorithm based on Grimberg 2016, a US Pediatric Endocrine Society guideline, as there are currently no Australian specific treatment guidelines for SPIGFD. As presented in Figure 1, if very low IGF-1 concentrations are observed together with GH sufficiency, mecasermin treatment is recommended if genetic causes of GH insensitivity are present or if GH trial has been tried unsuccessfully.

[2] Anderson LJ, Tamayose JM, et al. (2018). Use of growth hormone, IGF-I, and insulin for anabolic purpose: Pharmacological basis, methods of detection, and adverse effects. Mol Cell Endocrinol. 15;464: pp65-74.

Figure 1: Current & proposed clinical management algorithm



GH = growth hormone; GHBP = growth hormone binding protein; IGF-1 = insulin-like growth factor 1.
Source: Figure 1-2, p26 of the submission

4.9 The clinical management algorithm suggests using circulating levels of GH binding protein, IGF-1 generation test and mutation analyses in the screening phase. This is consistent with Grimberg 2016. However, these pathology tests were not included in the proposed PBS restrictions, inclusion criteria of clinical studies (except for mutation analyses), economic evaluation or financial estimates.

For more detail on PBAC's view, see Section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated no treatment as the comparator. This is reasonable considering that there are no other therapeutic alternatives. Patients with SPIGFD have GH sufficiency, therefore GH would not be an appropriate comparator.

For more detail on PBAC's view, see Section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health care professional. The input described a range of benefits of long term treatment with mecasermin including improved growth and potentially improved neurodevelopmental function including motor as well as social function.

Clinical studies/trials

6.3 The submission was based on one head-to-head trial comparing mecasermin to no treatment and three single-arm studies:

- Trial MS301: a one-year, randomised controlled, open-label trial (N=137). Treatment-naïve (not taken mecasermin previously) patients were randomised to receive no treatment or 40 µg/kg BID or 80 µg/kg BID mecasermin. Later, under Amendment 4 of the protocol, subjects in the 40 µg/kg BID group who had not already completed the study were reassigned to receive 120 µg/kg BID. Additional patients were recruited for the 120 µg/kg BID arm.
- Study 1419: a single-arm, open-label, non-randomised study assessing the effect of mecasermin until near-adult height (i.e., when the most recent bone age was at least 14 years old for females and 16 years old for males) in patients with primary IGFD associated with GH receptor defects or GH gene deletion defects and anti-GH antibodies (N=91). This study combined four previous studies, and 69 patients were recruited.
- EU-IGFD Registry: a single-arm, open-label, non-randomised study assessing the effect of mecasermin until near-adult height (N=281).
- Polish Study: a single-arm, open-label, non-randomised study assessing the effect of mecasermin in the first patients treated in Poland for three years (N=27).

6.4 Details of the trial and studies presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trial MS301	Recombinant human insulin-like growth factor-1 (rhIGF-1) treatment of pre-pubertal children with growth failure associated with primary IGF-1 deficiency: a Phase 3, randomised, open label, observation-controlled, multicentre, parallel-dose comparison trial	April 2011
	Midyett LK, Rogol AD, et al. Recombinant insulin-like growth factor (IGF)-I treatment in short children with low IGF-I levels: first-year results from a randomized clinical trial. [Identified during evaluation]	J Clin Endocrinol Metab. 2010 Feb;95(2):611-9.
Study 1419	A Study of Long-Term Recombinant Human Insulin-Like Growth Factor-1 (rhIGF-1) Treatment of Children with Short Stature Due to Severe Primary IGF-1 Deficiency Study. This is an Integrated Study Report Involving Five Individual Studies	July 2012
	Chernausek SD, Backeljauw PF et al. GH Insensitivity Syndrome Collaborative Group. Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity.	J Clin Endocrinol Metab. 2007 Mar;92(3):902-10

Trial ID	Protocol title/ Publication title	Publication citation
	Backeljauw PF, Kuntze J et al. Adult and near-adult height in patients with severe insulin-like growth factor-I deficiency after long-term therapy with recombinant human insulin-like growth factor-I.	Horm Res Paediatr. 2013;80(1):47-56
EU-IGFD Registry	European Increlex® (Mecasermin [RDNA origin] Injection) Growth Forum Database: A European Subject Registry for Monitoring Long-Term Safety and Efficacy of Increlex® - EU-IGFD	January 2020
	Bang P, Woelfle J, et al. Effectiveness and safety of rhIGF-1 therapy in patients with or without Laron syndrome. [Identified during evaluation]	Eur J Endocrinol. 2021 Feb;184(2):267-276
	Bang P, Polak M et al. EU IGFD Registry Study Group. Effectiveness and Safety of rhIGF-1 Therapy in Children: The European Increlex® Growth Forum Database Experience.	Horm Res Paediatr. 2015;83(5):345-57.
	Bang P, Polak M et al. Responders and poor-responders to Increlex® therapy: Data from the European Increlex® Growth Forum Database (EU-IGFD)	Eighth International Congress of the GRS and the IGF Society. Growth Hormone and IGF Research 2016; 30-31 Supplement 1: S34
	Bang P, Polak M et al. Pubertal growth dynamics in children with severe primary IGF-1 deficiency (SPIGFD): Results from the European Increlex® growth forum database (EU-IGFD)	10th Individual Abstracts for International Meeting of Pediatric Endocrinology. Horm Res Paediatr 2017; 88 (suppl 1): 489
	Polak M., Woelfle J. et al. Characteristics, effectiveness and safety data for patients with growth failure treated with recombinant IGF-I (RHIGF-I) and achieving adult or near-adult height (AH): Results from the European Increlex® growth forum database (EU-IGFD) Registry	57th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Horm Res Paediatr 2018;90 (suppl 1):1–680
	Woelfle J, Polak M, Hypoglycaemia adverse events in SPIGFD: Association with patient diagnosis, age, time-course and dosage of mecasermin: 10-year data from the European Increlex® growth forum database in Europe (EU-IGFD)	58th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Horm Res Paediatr 2019;91 (suppl 1):1–682
	Woelfle J, Polak M, Characteristics, effectiveness and safety data from clinically relevant subgroups of patients with severe primary IGF-i deficiency (SPIGFD): Results from the European Increlex® growth forum database (EU-IGFD) Registry	57th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Horm Res Paediatr 2018;90 (suppl 1):1–680
Polish Study	Petriczko E, Jackowski T et al. Treatment of severe primary IGF-1 deficiency using rhIGF-1 preparation - first three years of Polish experience.	Endokrynol Pol. 2019;70(1):20-27
	Petriczko E., Horodnicka-Jozwa A et al. Effects of the two-year treatment with recombinant IGF-1(rhIGF-1) of children with primary IGF-1 deficiency in Poland: A multicenter study	9th Joint Meeting of Paediatric Endocrinology. Horm Res Paediatr 2013;80(suppl 1):1-489

EU-IGFD = European Increlex® Growth Forum Database.
Source: Table 2-4, pp37-38 of the submission.

6.5 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Mecasermin vs. no treatment						
Trial MS301	137	R, OL, MC 1 year	Moderate[a]	PIGFD	Height velocity, HSDS	Not used
Study 1419	91	S, OL, MC Up to 19 years	Serious	PIGFD	Height velocity, height velocity SDS, HSDS,	Used
EU-IGFD Registry	281	S, OL, MC Up to 10 years	Serious	PIGFD	Height velocity, HSDS, height	Used
Polish Study	27	S, OL, MC 3 years	Moderate	Severe PIGFD	Height velocity, HSDS	Not used

EU-IGFD = European Increlex® Growth Forum Database; HSDS = height standard deviation score; MC = multi-centre; OL = open label; R = randomised; S = single-arm; SDS = standard deviation score; PIGFD = primary insulin-like growth factor deficiency.
Source: Table 2-8, p45 of the submission, Table 2-7, p44 of the submission; p47 of the submission; p48 of the submission; Table 3, p30 of 'Attachment 3c - EU-IGFD Registry CSR' of the submission; Table 2-9, p46 of the Submission.
[a] Revised after the evaluation.

6.6 The PBAC considered that Trial MS301 had a moderate risk of bias because the trial was open-label, however the risk of bias was not considered high because outcome measures relied on an objective outcome (patient height).

6.7 Study 1419 and the EU-IGFD Registry had a serious risk of bias according to the ROBINS-1 tool as each study had at least one domain with a serious risk of bias. Bias due to missing data was considered serious for Study 1419 and the EU-IGFD Registry, as withdrawal was significant (30/91 patients were lost to follow-up in Study 1419, and 46/281 in EU-IGFD Registry), and no imputation was performed for these patients. Other domains were deemed as low risk. The Polish Study had a moderate risk of bias due to the open-label design, which might bias height measurement.

6.8 The population in the trial and studies differed from the proposed PBS restriction:

- Trial MS301 included patients with HSDS <-2.0, IGF-1 standard deviation (SD) score <-2.0, patients aged 3-12 years, bone age ≤11 years for girls and ≤12 years for boys, pre-pubertal stage 2 or less, GH sufficiency and adequate nutrition. Patients with Laron Syndrome or GH gene deletion were excluded. The impact of excluding these patients is uncertain. Trial MS301 eligibility criteria differ from the proposed PBS restriction. The proposed PBS restriction included HSDS <-3.0 and different criteria for growth rate (height velocity less than the 25th percentile for bone age based on two measurements over 12 months) and IGF-1 levels (IGF-1 levels below the 2.5th percentile for age and gender). The mean baseline HSDS in Trial MS301 was -2.8 (max -1.7), which suggests that a large proportion of patients in the trial did not satisfy the PBS restriction and neither would they be eligible for treatment according to the TGA-approved indication.
- Study 1419 included patients with HSDS <-2.0 for age and sex, growth rate <50th percentile for age and sex, IGF-1 SD score <-2.0, age > 18 months, diagnosis of growth hormone insensitivity syndrome (GHIS) caused by Laron syndrome or GH

gene-deletion type. The Study 1419 eligibility criteria differed from the proposed PBS restriction. The proposed PBS restriction included HSDS <-3.0 and different criteria for growth rate (height velocity less than the 25th percentile for bone age based on two measurements over 12 months) and IGF-1 levels (IGF-1 levels below the 2.5th percentile for age and gender). However, the mean baseline HSDS in Study 1419 was -6.9 (max -2.8), consistent with the proposed PBS restriction.

- The EU-IGFD Registry included all subjects starting mecasermin therapy for growth retardation and subjects previously treated with mecasermin prescribed by a participating qualified practitioner with informed consent for Registry activities. Specific criteria such as HSDS, height velocity, IGF-1 levels, GH sufficiency, or secondary causes of SPIGFD were not included.
- The Polish study included patients with HSDS <-3.0 and IGF-1 concentration below percentile 2.5 with normal GH levels. This did not include height velocity or exclusion of secondary causes of SPIGFD. HSDS, IGF-1 levels and GH criterion were consistent with the PBS restriction.
- Fifteen percent of patients in the EU-IGFD Registry had Laron syndrome, whereas 89% had Laron syndrome in Study 1419. The implications of this are uncertain.

6.9 A sub-group analysis considering only patients with HSDS <-3.0 was not presented, particularly for Trial MS301 that had a mean (SD) HSDS of -2.8 (0.7). A sub-group analysis would be in line with the requested PBS restriction.

6.10 The sample size of Trial MS301 was small (n=136), and follow-up at one year was very limited relative to the duration over which patients would be treated (up to 16 years).

6.11 The pre-PBAC response also acknowledged that limited data are available beyond the key efficacy evidence that was included in the submission which was derived from registration trials that used height velocity as the primary outcome variable. With regard to treatment benefits other than height, the pre-PBAC response described the presentation of children with SPIGFD and described negative social impacts associated with the condition, which may be experienced in childhood and throughout adult life. The pre-PBAC response also referred to treatment benefits beyond growth velocity including bone maturation, organ growth, metabolic risks such as obesity and hypercholesterolemia, hypoglycaemia and hyperglycaemia, and psychosocial wellbeing.

Comparative effectiveness

6.12 Effectiveness results for the primary outcome (height velocity) for Trial MS301 is presented in Table 4 and for the single-arm studies are presented in Table 5. The submission did not indicate what difference in height velocity was considered to be clinically meaningful. However, Bang 2021 defined responders to mecasermin if a change in HSDS in year one of ≥0.3 was observed.

Table 4: Height velocity (cm/year) during the first year of treatment, Trial MS301, ITT population

		Untreated control N=22	Mecasermin 80 µg/kg BID N=42	Mecasermin 120 µg/kg BID N=49
Actual values	Mean (SD)	5.2 (1.0)	6.9 (1.0)	7.7 (1.5)
Mecasermin vs untreated control	LS mean difference (95% CI)	-	1.79 (1.19, 2.39)	2.58 (1.99, 3.16)
	p-value	-	**<0.0001**	**<0.0001**
Mecasermin 120 vs 80 µg/kg	LS mean difference (95% CI)	-	-	0.79 (0.27, 1.31)
	p-value	-	-	**0.0032**

BID = twice-daily; CI = confidence interval; ITT = intention to treat; LS = least squares; SD = standard deviation
Source: Table 2-30, p69 of the submission.
Note: Results presented in **bold** are statistically significant.

Table 5: Annualised height velocity (cm/year) change from pre-treatment by treatment year, single-arm studies.

Treatment year	Study 1419[a]			EU-IGFD Registry[b]				Polish Study[c]		
	N	Mean height velocity (SD)	Mean (SD) change from pre-treatment	N	Mean height velocity (SD)	N	Mean (SD) change from pre-treatment	N	Mean height velocity (SD)	Mean change from pre-treatment
Pre-treatment	75	2.6 (1.7)	NA	151	4.69 (1.73)	NA	NA	25	4.5 (1.6)	NA
Year 1	75	8.0 (2.3)	**5.4 (2.6)**	197	6.87 (2.26)	123	**2.03 (2.57)**	25	7.8 (1.9)	**3.3**
Year 2	63	5.9 (1.7)	**3.2 (2.6)**	138	6.08 (1.93)	82	**1.35 (2.35)**	25	6.3 (0.8)	**1.8**
Year 3	62	5.5 (1.8)	**2.8 (2.4)**	110	5.62 (2.12)	61	**0.73 (2.78)**	25	4.9 (1.8)	0.4
Year 4	60	5.2 (1.5)	**2.5 (2.5)**	74	5.34 (1.78)	36	0.51 (2.23)			
Year 5	53	4.9 (1.5)	**2.1 (2.1)**	47	5.00 (1.75)	23	0.23 (1.85)			
Year 6	39	4.8 (1.4)	**1.9 (2.1)**	37	5.04 (1.89)	22	-0.35 (2.64)			
Year 7	25	4.3 (1.5)	**1.4 (2.3)**	21	5.29 (2.34)	12	0.10 (3.11)			
Year 8	19	4.4 (1.5)	**1.3 (2.8)**	14	5.65 (2.45)	8	-0.51 (2.67)			
Year 9	14	4.4 (1.7)	1.1 (3.2)	6	3.15 (1.79)	2	NR			
Year 10	13	4.5 (2.0)	1.1 (3.5)	3	4.34 (1.27)	1	NR			
Year 11	12	4.1 (2.0)	0.7 (3.3)							
Year 12	10	3.9 (2.0)	-0.1 (3.2)							
Year 13	9	3.3 (1.7)	-0.2 (2.0)							
Year 14	6	2.3 (1.6)	-2.1 (2.9)							
Year 15	4	3.1 (1.8)	-1.0 (3.1)							
Year 16	3	2.9 (1.4)	-0.8 (1.6)							
Year 17	2	1.7 (0.8)	-3.3 (0.7)							
Year 18	1	0.2 (NA)	-5.8 (NA)							
Year 19	1	0.2 (NA)	-5.8 (NA)							

N = number of subjects completing years of treatment; NA = not applicable; SD = standard deviation
Source: Table 2-26, p63 of the submission; Table 2-31, p70 of the submission; Table 2-32, p72 of the submission.
Note: Results presented in **bold** are statistically significant. Comparison of each year was made against patients still enrolled in the study at the time of measurement, i.e., the 62 patients in year 3 of Study 1419 were compared against those 62 patients' values at baseline.
[a] Baseline age range 1.7-15.2
[b] Baseline age range 0.4-19.1
[c] Calculated by the submission. Details of how this was estimated were not provided. Baseline age range 2.8-16.2

6.13 Trial MS301 provided the only within-trial comparison of mecasermin versus no treatment in a randomised, open-label design. However, the trial duration was only one year. The difference in height velocity from baseline and the difference between

no treatment and 80 µg/kg BID and 120 µg/kg BID were both statistically significant in Trial MS301.

6.14 The difference in height velocity from baseline in Study 1419 was statistically significant from year one to eight. This was also true for the first three years in the EU-IGFD Registry and the first two years in the Polish Study ($p<0.05$). The highest increase in height velocity was observed in year one in each study. The height velocities versus control for the first treatment year in Trial MS301 (1.79 cm/year for 80 µg/kg BID and 2.58 for 120 µg/kg BID) were similar to the velocities versus pre-treatment in the EU-IGFD Registry (2.03 cm/year), but substantially lower than Study 1419 (5.4 cm/year). A similar trend was observed with HSDS between Trial MS301, Study 1419 and the EU-IGFD Registry (Table 6), which was sustained for more extended periods. The Bang 2021 criterion for mecasermin responders was met in Trial MS301, Study 1419 and the EU-IGFD Registry. The Polish study did not report year one data.

6.15 The ESC noted that Study 1419 had the longest follow-up period and showed reducing HSDS over time, indicating that patient height was gradually approaching the height of the age- and sex-matched general population with continued mecasermin treatment (Table 6).

Table 6: Change in height standard deviation score from pre-treatment by treatment year

Treatment year	Study 1419[a]			EU-IGFD Registry[b]				Polish Study[c]		
	N	Mean HSDS (SD)	Mean (SD) change from pre-treatment	N	Mean HSDS (SD)	N	Mean (SD) change from pre-treatment	N	Mean HSDS (SD)	Mean change from pre-treatment
Pre-treatment	81	-6.9 (1.8)		249	-3.79 (1.34)	NA	NA	25	-3.52 (0.82)	NA
Year 1	81	-6.1 (1.8)	**0.8 (0.6)**	225	-3.46 (1.36)	204	**0.35 (0.46)**	25	NR	NR
Year 2	67	-5.6 (1.7)	**1.2 (0.9)**	176	-3.26 (1.48)	161	**0.66 (0.67)**	25	NR	NR
Year 3	66	-5.3 (1.7)	**1.4 (1.1)**	131	-3.04 (1.62)	119	**0.81 (0.72)**	25	**-2.25 (0.91)**	**NR**
Year 4	64	-5.1 (1.7)	**1.6 (1.2)**	97	-2.99 (1.67)	87	**0.98 (0.68)**			
Year 5	57	-5.0 (1.7)	**1.7 (1.3)**	70	-2.79 (1.82)	62	**1.08 (0.78)**			
Year 6	41	-4.9 (1.6)	**1.8 (1.1)**	50	-3.01 (1.92)	46	**1.01 (0.82)**			
Year 7	26	-4.9 (1.7)	**1.7 (1.0)**	29	-2.70 (1.97)	25	**1.22 (0.87)**			
Year 8	19	-5.1 (1.7)	**1.7 (1.0)**	19	-2.86 (2.12)	17	**1.33 (1.04)**			
Year 9	14	-5.0 (1.6)	**1.8 (0.9)**	9	-3.01 (1.58)	7	**1.39 (0.71)**			
Year 10	13	-5.0 (1.7)	**1.9 (1.0)**	4	-3.34 (1.75)	2	NR			
Year 11	12	-4.7 (1.2)	**1.9 (1.0)**							
Year 12	10	-4.4 (1.3)	**2.0 (0.9)**							
Year 13	9	-4.7 (1.0)	**2.1 (0.9)**							
Year 14	6	-4.3 (1.0)	**2.3 (1.0)**							
Year 15	4	-4.7 (1.6)	1.9 (1.5)							
Year 16	3	-4.0 (1.5)	2.2 (1.9)							
Year 17	2	-3.4 (2.0)	3.0 (2.4)							
Year 18	1	-2.0 (NA)	4.7 (NA)							
Year 19	1	-1.9 (NA)	4.7 (NA)							

HSDS = height standard deviation score; N = subjects completing years of treatment; NA = not applicable; SD = standard deviation
Source: Table 2-28, p66 of the submission; p70 of the submission; Table 2-33; p73 of the submission (Table 2.5.5: in the Commentary).
Note: Results presented in **bold** are statistically significant. Results presented in italics were corrected in the Commentary. Comparison of each year was made against patients still enrolled in the study at the time of measurement, i.e., the 62 patients in year 3 of Study 1419 were compared against those 62 patients' values at baseline.
[a] Baseline age range 1.7-15.2
[b] Baseline age range 0.4-19.1
[c] Calculated by the submission. Details of how this was estimated were not provided. Baseline age range 2.8-16.2

6.16 The submission presented three subgroup analyses:

1. A separate analysis was conducted in Study 1419 for mecasermin naïve subjects (n=52), excluding subjects enrolled in the previous four studies that received mecasermin. Results for height velocity were slightly higher in each treatment year compared to the whole trial population.
2. A subgroup analysis of the EU-IGFD Registry was conducted for pre-pubertal subjects only (n=118). Results for height velocity were slightly higher in each treatment year compared to the whole trial population.
3. The submission presented an analysis comparing patients that attained near-adult height to what would be expected from patients with Laron syndrome without treatment. An estimated improvement in height of 13.4 (9.9-16.6 95% CI) centimetres after an average of 11 years of treatment was observed.

Comparative harms

6.17 Table 7 presents the safety results of mecasermin in Trial MS301, Study 1419 and the EU-IGFD Registry.

6.18 The submission noted that the Polish Study did not present comprehensive safety data other than reporting eight (30%) patients having an adverse event (AE) over the three-year study (p74 of the submission). Two of these patients ended treatment before year three because of an AE.

Table 7: Summary of key adverse events in Trial MS301, Study 1419 and the EU-IGFD Registry

Category	Trial MS301				Study 1419	EU-IGFD Registry
	Untreated	Mecasermin 40 µg/kg BID	Mecasermin 80 µg/kg BID	Mecasermin 120 µg/kg BID		
N	25	16	44	51	92	277
Mean duration of treatment (years)	1.0	1.0	0.9	0.9	6.0	3.7
Any adverse event	23 (92%)	16 (100%)	40 (91%)	50 (98%)	76 (83%)	185 (67%)
Serious adverse event	1 (4%)	1 (6%)	2 (5%)	5 (10%)	18 (20%)	59 (21%)
Treatment-related adverse event	0	9 (56%)	23 (52%)	31 (61%)	68 (74%)	141 (51%)
Adverse event leading to discontinuation	0	0	2 (5%)	5 (10%)	0	15 (5%)
Death	0	0	0	0	0	2 (1%)

BID = twice daily; EU-IGFD = European Increlex® Growth Forum Database.
Source: Table 2-35, p75 of the submission.

6.19 A statistical analysis presented by the submission noted that, in Trial MS301, the rates of AE, serious AE (SAE), AE leading to withdrawal, and deaths were not statistically significantly higher in any of the mecasermin groups compared to the untreated group. The submission provided no further description of the analysis method. The submission claimed that all SAE were resolved by the end of the Trial MS301.

6.20 Study 1419 and the EU-IGFD Registry reported that 20% and 21% of subjects, respectively, had at least one SAE. These rates were substantially higher than in all arms of Trial MS301. However, follow-up times differed (6.0 years for Study 1419 and 3.7 years for the EU-IGFD Registry). The most common SAE in Study 1419 were adenoidal hypertrophy with 3 events, and tonsillar hypertrophy and appendicitis both with 2 events, whereas for the EU-IGFD Registry the common SAEs were hypoglycaemia presenting 12 events, tonsillar hypertrophy with 5 and adenoidal hypertrophy with 4.

6.21 Two deaths occurred in the EU-IGFD Registry. These were not described in the submission but were reported in the clinical study report (CSR). One of them was deemed as not related to mecasermin (severe complications of a bone marrow transplant, three years after discontinuing mecasermin). The second event was considered as not related to mecasermin by the investigator but assessed as treatment related by the Sponsor based on the data review committee conclusions (myelodysplastic syndrome, 1.6 years after mecasermin initiation).

6.22 The submission conducted a statistical analysis on Trial MS301, showing that rates of 'metabolism and nutrition disorders', 'general disorders and administration site conditions', 'gastrointestinal disorders' and 'nervous system disorders' were statistically significantly higher with any of the mecasermin doses compared to the untreated group. The submission provided no further description of the analysis method.

6.23 The submission noted that the most frequent AE was hypoglycaemia (related to metabolism and nutrition disorders) but was avoidable considering meals timing with mecasermin administration. However, seven subjects in Study 1419 presented severe hypoglycaemia and seven presented hypoglycaemic seizures. The TGA had noted that the main safety concern was hypoglycaemia. The ESC considered that hypoglycaemia could be managed, however education of patients and carers would be important, highlighting the need for a Quality Use of Medicine Program.

6.24 The EU signal report noted a neoplasia incidence rate 4.5 times higher than the normal population for mecasermin users. However, the TGA Clinical Evaluation Report stated that patients that developed neoplasia were using mecasermin for reasons other than SPIGFD, had other risk factors for malignancy, or used doses higher than recommended.

6.25 The US Pediatric Endocrine Society guideline published by Grimberg 2016 (p386) notes that other than hypoglycaemia, the potential side effects of IGF-1 treatment are similar to those of GH including: intracranial hypertension, slipped capital femoral epiphysis (SCFE), and progression of scoliosis. As for GH, IGF-1 treatment is contraindicated in patients with active malignancy. In addition, the guideline notes the following potential side effects of IGF-1 treatment: lymphoid tissue hypertrophy (such as enlargement of tonsils and adenoids), hypersensitivity/allergic reactions, and reactions to the benzyl alcohol component of the diluent.

Benefits/harms

6.26 A summary of the comparative benefits and harms for mecasermin versus no treatment is presented in the table below.

Table 8: Summary of comparative benefits and harms for mecasermin and no treatment

Continuous outcome I: change from baseline height velocity (cm/year) at year 1							
Trial/Study	Mecasermin			No treatment			Mean difference: mecasermin vs. no treatment (95% CI)
	N	Mean Δ baseline height velocity	SD	N	Mean Δ baseline height velocity	SD	
Trial MS301 80 µg/kg BID	42	NR	NR	22	NR	NR	1.79 (1.19, 2.39)
Trial MS301 120 µg/kg BID	49	NR	NR				2.58 (1.99, 3.16)
Study 1419	75	5.4	2.6	NA	NA	NA	NA
Polish Study	25	3.3	NR	NA	NA	NA	NA
EU-IGFD Registry	123	2.03	2.57	NA	NA	NA	NA

Harms[a]						
	Mecasermin n/N	No treatment n/N	RR[b] (95% CI)	Event rate/100 patients		RD[b], % (95% CI)
				Mecasermin	No treatment	
Adverse event I: Metabolism and nutrition disorders						
Trial MS301 40 µg/kg BID	2/16	2/25	1.56 (0.24, 10.01)	12.50	8.00	4.5% (-14.88, 23.88)
Trial MS301 80 µg/kg BID	8/44		2.27 (0.52, 9.88)	18.18		10.18 (-5.41, 25.77)
Trial MS301 120 µg/kg BID	17/51		4.18 (1.04, 16.64)	33.33		25.33 (8.59, 42.08)
Study 1419	48/92	NA	NA	52.17	NA	NA
EU-IGFD Registry	73/277	NA	NA	26.35	NA	NA
Adverse event II: General disorders and administration site conditions						
Trial MS301 40 µg/kg BID	9/16	5/25	2.81 (1.15, 6.89)	56.25	2.00	36.25 (7.32, 65.18)
Trial MS301 80 µg/kg BID	26/44		2.96 (1.30, 6.72)	59.09		39.09 (17.72, 60.47)
Trial MS301 120 µg/kg BID	27/51		2.65 (1.16, 6.04)	52.94		32.94 (12.12, 53.76)
Study 1419	42/92	NA	NA	45.65	NA	NA
EU-IGFD Registry	32/277	NA	NA	11.55	NA	NA
Adverse event III: Gastrointestinal disorders						
Trial MS301 40 µg/kg BID	12/16	3/25	6.25 (2.08, 18.75)	75.00	12.00	63.00 (38.25, 87.75)
Trial MS301 80 µg/kg BID	18/44		3.41 (1.11, 10.44)	40.91		28.91 (9.59, 48.23)
Trial MS301 120 µg/kg BID	27/51		4.41 (2.19, 31.06)	52.94		40.94 (22.23, 59.65)
Study 1419	33/92	NA	NA	35.87	NA	NA
EU-IGFD Registry	13/277	NA	NA	4.69	NA	NA
Adverse event IV: Nervous system disorders						
Trial MS301 40 µg/kg BID	9/16	4/25	3.52 (1.30, 9.53)	56.25	16.00	40.25 (12.01, 68.49)
Trial MS301 80 µg/kg BID	15/44		2.13 (0.79, 5.72)	34.09		18.09 (-1.98, 38.16)
Trial MS301 120 µg/kg BID	23/51		2.82 (1.09, 7.27)	45.10		29.10 (9.27, 48.92)
Study 1419	31/92	NA	NA	33.70	NA	NA
EU-IGFD Registry	38/277	NA	NA	13.72	NA	NA

CI = confidence interval; NA = not applicable; NR = not reported; RD = risk difference; RR = risk ratio

Source: Table 2-26, p63 of the submission; Table 2-31, p70 of the submission; Table 2-32, p72 of the submission; Table 2-30, p69 of the submission; Table 2-36, p76 of the submission

[a] Only statistically significant events by system organ class were added.

[b] RR and RD were calculated during the evaluation.

6.27 Based on the direct comparative evidence presented by the submission (MS301), the comparison of mecasermin and no treatment resulted in:

- Approximately a 1.79 cm per year improvement in height velocity over a maximum duration of follow-up of 12 months for 80 µg/kg BID dosing.

- Approximately a 2.58 cm per year improvement in height velocity over a maximum duration of follow-up of 12 months for 120 µg/kg BID dosing.

6.28 Based on the evidence presented in the submission, treatment with mecasermin resulted in an increase in adverse events classified as 'metabolism and nutrition disorders', 'general disorders and administration site conditions', 'gastrointestinal disorders' and 'nervous system disorders'. It was not possible to quantify the extent of the increase in specific events.

Clinical claim

6.29 The submission described mecasermin as superior in terms of effectiveness compared with no treatment, based on changes in height over time and near-adult height.

6.30 Each single-arm study and Trial MS301 showed improvement in height velocity, either compared to pre-treatment (single-arm studies) or compared to control treatment (Trial MS301). This improvement was sustained at least for three years in single-arm studies. The height velocity and HSDS in trial MS301 after one year of mecasermin treatment was similar to the EU-IGFD Registry but lower than Study 1419. The following issues were identified:

- There was only one randomised trial of mecasermin versus no treatment. This trial was small (n=137) and the follow-up at one year was limited relative to the duration over which patients would be treated (up to 16 years). Trial MS301 switched patients from the 40 µg/kg BID group to the 120 µg/kg BID group due to the 40 µg/kg BID not reaching adequate serum IGF-1 levels. However, the lack of randomised trials is reasonable considering the rarity of the condition.
- Three single-arm studies were also presented. Study 1419 and the EU-IGFD Registry included patients with HSDS <-2.0, which hinders their applicability to the proposed PBS restriction (HSDS <-3.0). The number of patients that did not meet the PBS restriction in Study 1419 was not described. However, this number is expected to be low as the mean HSDS was -6.8 (minimum -2.8). The EU-IGFD Registry included 36 such patients out of a total of 281 patients. A Polish Study was also presented. However, it had a small sample size (N=27).

6.31 The submission described mecasermin as non-inferior in terms of safety compared to no treatment, based on overall AE and SAE rates. The following issues were identified:

- Trial MS301 was the only comparative study and found that patients in at least one of the three mecasermin treatment arms had statistically significantly more AEs compared to the control arm in different system organ class, such as 'metabolism and nutrition disorders', 'general disorders and administration site conditions', 'gastrointestinal disorders' and 'nervous system disorders'.
- One death was associated with mecasermin treatment in the EU-IGFD Registry (patient developed myelodysplastic syndrome).

6.32 The PBAC considered that the submission's claim of superior comparative effectiveness was reasonable however the claim of non-inferior comparative safety was not adequately supported by the data. The PBAC considered that mecasermin has inferior safety when compared with no treatment based on MS301, with reported adverse events including hypoglycaemia, headache, tonsil enlargement and vomiting (Midyett 2010, p616). PBAC also noted the potential neoplasia risk described in the TGA product information.

Economic analysis

6.33 The submission presented a cost-utility analysis comparing mecasermin with no treatment. A stepped economic evaluation was presented based on two single-arm studies, EU-IGFD Registry (base case) and Study 1419 (sensitivity analysis).

6.34 Key components of the economic model are presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Population	Proposed PBS restriction: 2-18 years (inclusive) The economic model included 36 different cohorts: 18 cohorts for each arm (mecasermin and no treatment) defined by treatment starting ages ranging between 2 and 10 years and biological sex. Total costs, QALYs, and ICERs were calculated for each cohort over a lifetime horizon and weighted according to chronological age and biological sex starting distributions. The minimum treatment start age was 2 years old and the maximum treatment time permitted by the model structure was 19 years. The economic model varies from the proposed PBS restriction which allows mecasermin treatment for children aged 2 to 18. The model assumed 90% of the children starting treatment at age 2 and the remaining 10% at age 5. This does not capture the full range of proposed PBS population.
Time horizon	Lifetime (100 years). The lifetime time horizon was long compared to the duration of follow-up in Study 1419 and the EU-IGFD Registry (until near adult age). The ICER was mildly sensitive to a shorter time horizon of 50 years ([redacted][1] / QALY gained) and highly sensitive to a 25-year time horizon ([redacted][2] / QALY gained), versus [redacted][1] /QALY gained in the base case.
Outcomes	QALYs gained
Methods used to generate results	Decision analytic model
Health states	On treatment, not on treatment, dead
Cycle length	One year
Transition probabilities	Discontinuation and adverse event rates: Based on the EU-IGFD Registry (base case) and Study 1419 (sensitivity analysis). Mortality rates: General mortality was based on Australian life expectancy tables for treated and untreated groups. Height velocity, untreated patients: Laron 1993 study Height velocity, mecasermin treated patients: the EU-IGFD Registry (treatment naïve prepubertal patients). The relative treatment effect between mecasermin and no treatment was based on an unrandomised, unadjusted naïve comparison. Trial MS301 provided the only within-study comparison of mecasermin

Component	Summary
	versus no treatment in a randomised, open-label design. However, the trial duration was only one year. The height velocity in trial MS301 after one year of mecasermin treatment was similar to EU-IGFD but slightly lower than Study 1419. The submission did not justify using the EU-IGFD Registry in the base case. Study 1419 had potentially more relevant inclusion criteria than EU-IGFD in terms of HSDS, growth hormone sufficiency and exclusion of secondary forms of IGF-1 deficiency. The HSDS scores in Study 1419 (-6.9, range: -12.1, -2.8) were closer to those in the proposed PBS restriction (≤-3.0) than those in EU-IGFD (mean -3.8, range: -9.4 to -1.3). For the untreated patients, a change in height from one year to the next was used in the model. For the mecasermin treated patients, instead of the change in height from the pre-treatment height, the yearly mean absolute height values from the EU-IGFD registry were implemented as the baseline values for each age cohort. Although the submission did not discuss or justify this assumption, it was probably due to the different treatment ages in the mecasermin treated patients and the differences in baseline height. For example, the pre-treatment baseline mean height in EU-IGFD was 114 cm (mean age 9.5 years) compared with 88 to 100 cm in the Laron 1993 (untreated) cohort (for patients aged 9 to 10). Although the absolute height gains were superior in the EU-IGFD Registry than Study 1419, the reverse was true when comparing the change in height from the pre-treatment baseline. This approach introduces structural uncertainty. No sensitivity analysis was conducted on this approach. HSDS values: Based on WHO height charts for the general population for the treated and untreated groups. Probability of an AE: The AEs associated with mecasermin treatment were based on the EU-IGFD Registry. Some common adverse events presented in the safety analysis were not included in the model, and a justification for their exclusion was also not provided. These included snoring, sleep apnoea, myalgia, and arthralgia. Inclusion of the costs associated with managing these adverse events will potentially increase the total cost. However, these costs are likely to be small. One death was associated with mecasermin treatment in the EU-IGFD Registry. This was not discussed or modelled in the submission.
Health-related quality of life	Utilities: Utilities were based on a published study (Christensen 2007), which analysed the utility (measured with EQ-5D) of the UK general population. The relationship between qualify of life and HSDS was extrapolated for HSDS less than -3.5. Disutilities associated with adverse events from mecasermin treatment were not included in the model.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; HSDS = height standard deviation score; WHO = World Health Organisation; UK = United Kingdom; SPIGFD = severe primary insulin-like growth factor deficiency; AE = adverse event.
Source: Table 3-1, p90 of the submission.
The redacted values correspond to the following ranges:
[1] $95,000 to < $115,000
[2] $135,000 to < $155,000

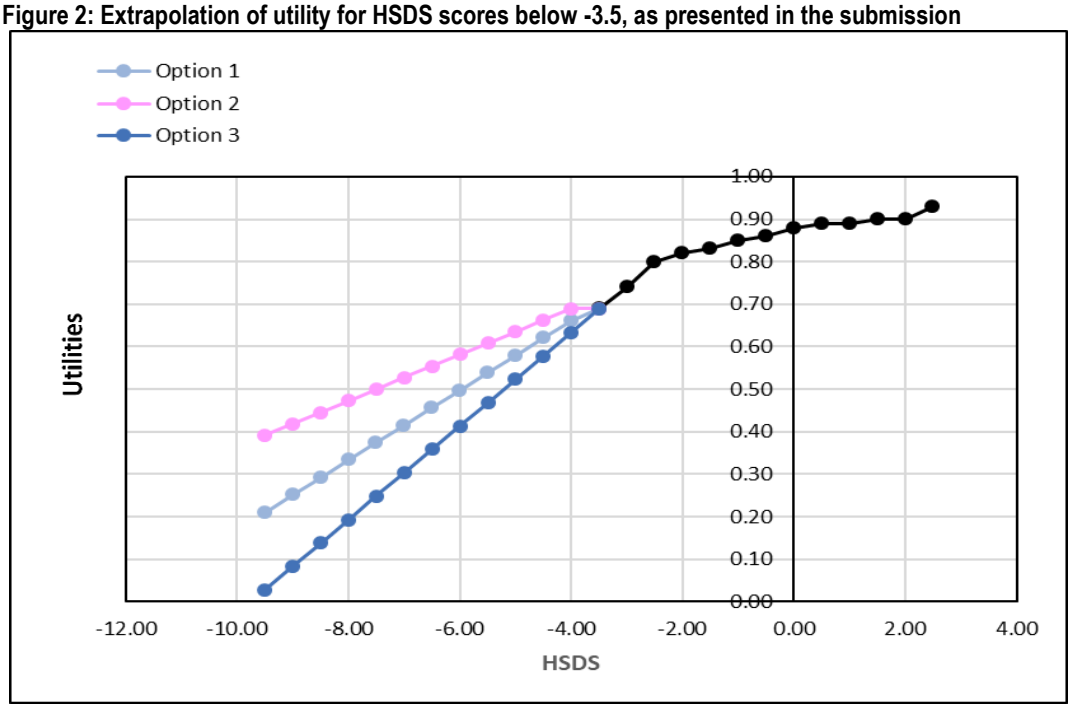
6.35 The submission did not justify the choice of efficacy data from the EU-IGFD Registry in the base case. Using Study 1419 (treatment naïve subgroup) as the base-case for treatment discontinuation rates, mecasermin dosing, adverse events, and height gain increased the ICER from $95,000 to < $115,000 to $115,000 to < $135,000 per QALY gained (values reflect submission model).

6.36 All incremental QALYs were estimated from differences in QoL between the mecasermin treated versus no treatment arms, as life expectancy was assumed equal between treatment arms.

6.37 Utilities were based on a published study (Christensen 2007)[3], which analysed the utility (measured with EQ-5D) of the UK general population. A literature search conducted during the evaluation found no other relevant studies.

6.38 The relationship between qualify of life and HSDS was extrapolated for HSDS less than -3.5 (see Figure 2). In the base case ("Option 1"), the submission assumed the slope of the relationship between utilities and HSDS, observed over HSDS -3.5 to 0, steepened for HSDS ≤-3. The upper limit (Option 2) was based on a linear trend using the relationship of HSDS and utility from the Christensen 2007 study when HSDS was less than zero. The lower limit (Option 3) represented a steeper decline in utility when HSDS was less than -3.5.

Figure 2: Extrapolation of utility for HSDS scores below -3.5, as presented in the submission



HSDS = height standard deviation score; QALYs = Quality adjusted life years.
Source: Figure 3-5, p114 of the submission.

6.39 The method of extrapolation from the data reported by Christensen 2007 was not well supported. It is unknown whether a linear trend is reflective of scores below -3.5 standard deviations (Figure 2).

6.40 In comparison with the base case (Option 1), the evaluation considered Option 2 more suitable because it is consistent with the observed data over HSDS -3.5 to 0, and there is insufficient evidence to assume the slope of utility as a function of HSDS steepens for HSDS <-3.5.

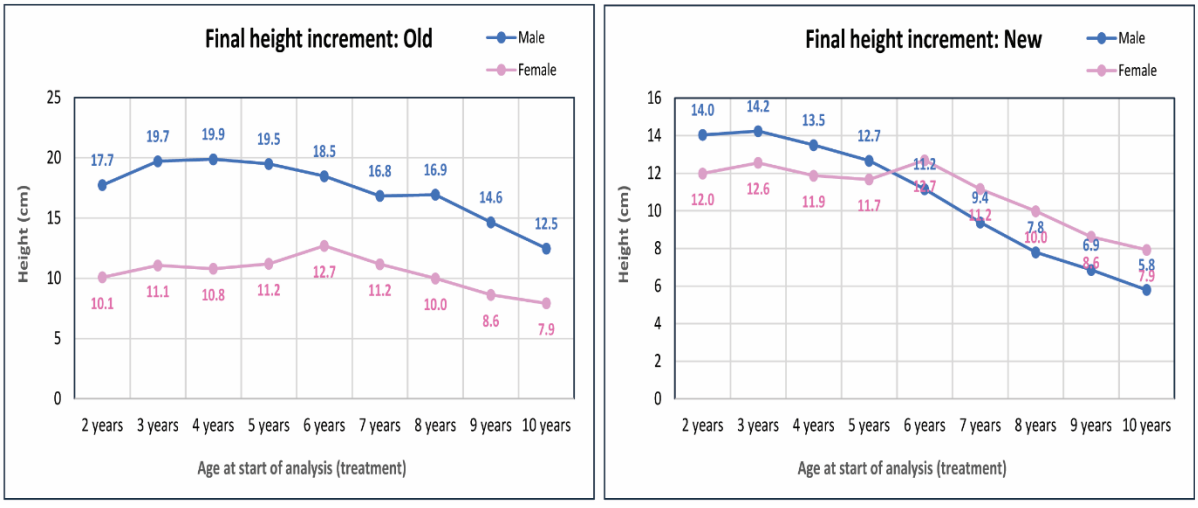
[3] Christensen TL, Djurhuus CB, Clayton P, Christiansen JS. An evaluation of the relationship between adult height and health-related quality of life in the general UK population. Clinical endocrinology. 2007 Sep;67(3):407-12.

6.41 The estimated utilities of people with SPIGFD were uncertain as 1) they were elicited from people in the general population, not from those with SPIGFD; 2) the height of the great majority of patients under the requested PBS restriction (≤-3.0 HSDS) was shorter than the shortest respondent in Christensen 2007 (-3.5); and 3) the utility values applied to children age 2 onwards were based on a survey of adults (aged ≥18 years). Overall, the lack of data from prospective longitudinal follow-up studies makes inferences about cause and consequences difficult. Ideally, a randomised study measuring utilities over time in the untreated and mecasermin treated patients would rule out the effects of any confounding variables on height and QoL. However, this information is not available.

6.42 A new version of the economic model was provided with the PSCR to correct a structural error that was identified during the evaluation. As noted in the PSCR, the original model incorrectly adjusted the average growth velocity for children depending upon whether they were on treatment or had discontinued, because the manner in which the growth velocity was adjusted ignored the historical growth profile of patients who continued on treatment, versus those who had discontinued. The PSCR states that the amended model demonstrates a greater level of face validity in the estimates produced, and better aligns with the clinical opinion that outcomes would be expected to be better in children who commence treatment earlier.

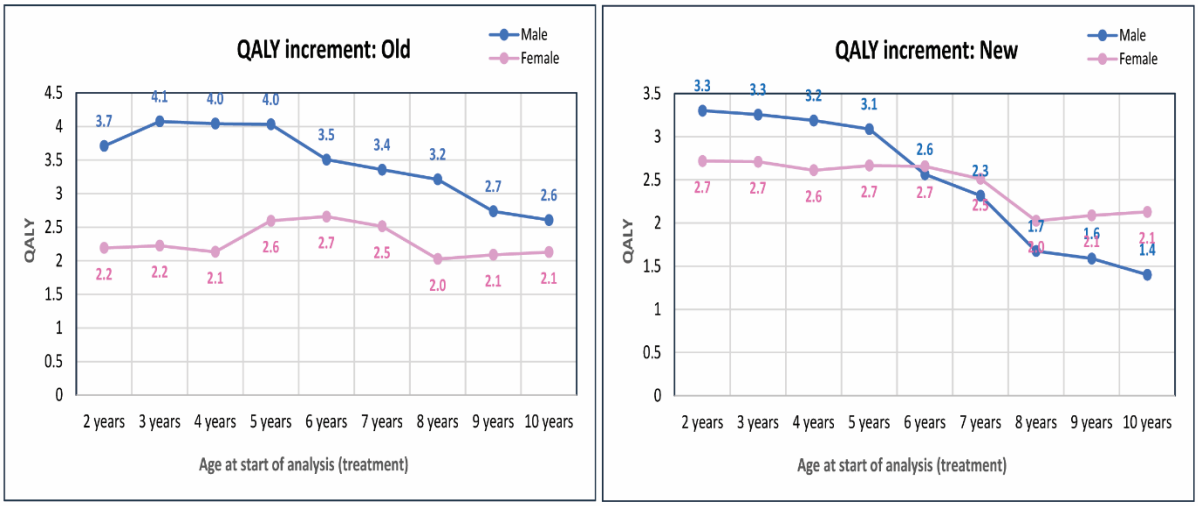
6.43 A comparison of the old and new results for the final height increase and associated QALY increment is provided in Figures 3 and 4 below. In the new model, the highest utility gains for males were reported at age 2 (3.3 vs. 4.1 at age 3 in the older model), followed by a downward trend from year 5 onwards (Figure 4). The height increment and the associated utility gains in the new model are lower than the older version for males. The results in the new version remain counter-intuitive for females as a biphasic trend is still apparent. The estimated QALY gains remain very uncertain given the inherent weaknesses of the QoL study used for utility estimation, as discussed above.

Figure 3: Final height difference in mecasermin treated minus untreated cohorts in the original versus new model



Source: 'Deterministic' workbook, Economic model workbook.

Figure 4: QALY increase in mecasermin treated minus untreated cohorts in the original versus new model



QALY = quality-adjusted life year.
Source: 'Deterministic' workbook, Economic model workbook.

6.44 Table 10 below presents the key drivers of the model based on the new version of the economic model provided with the PSCR. Key drivers of the model included: utility inputs, the EU-IGFD Registry for height velocity, treatment discontinuation, mecasermin dosing and treatment-related AEs.

Table 10: Key drivers of the model (updated to reflect new economic model)

Description	Method/Value	Impact Base case: [redacted][1]/QALY gained
Utilities	Steep slope in the utility / HSDS function extrapolated from the literature	High, favours mecasermin Using the preferred Option 2 in Figure 2 above increased the ICER to [redacted][2]/QALY gained.
Height velocity	Change in heights from one year to the next were taken from the EU-IGFD Registry	Moderate, favours mecasermin Applying the height velocities from Study 1419 increased the ICER to [redacted][3]/QALY gained.
Study 1419 data	Study 1419 informing probabilities related to treatment-related adverse events, mecasermin dosing, treatment discontinuation rate and height velocity	High, favours mecasermin Using Study 1419 instead of EU-IGFD Registry as the base-case for treatment discontinuation, mecasermin dosing, adverse events, and height velocity increased the ICER from [redacted][1] to [redacted][2]/QALY gained.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; HSDS = height standard deviation score.
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$135,000 to < $155,000*
[3] *$115,000 to < $135,000*

6.45 The PSCR provided an updated stepped economic analysis using the corrected model and base case using EU-IGFD Registry data (Table 11), which includes the following steps:

Step 1: Mean follow up time of EU-IGFD Registry (3.7 years), no treatment discontinuation, and mecasermin drug cost only.

Step 2: Mean follow up time of EU-IGFD Registry (3.7 years), treatment discontinuation, and mecasermin drug cost only.

Step 3: Lifetime time horizon, treatment discontinuation, and mecasermin drug cost only.

Step 4: Lifetime time horizon, treatment discontinuation, and all costs.

Table 11: Updated stepped economic evaluation (as presented in the PSCR)

Step	Costs ($)			Outcomes (QALYs)			ICER (cost per QALY gained) ($)
	Mecasermin	No mecasermin	Incremental	Mecasermin	No mecasermin	Incremental	
Step 1	[redacted]	0	[redacted]	1.44	1.27	0.17	[redacted][1]
Step 2	[redacted]	0	[redacted]	1.44	1.27	0.17	[redacted][1]
Step 3	[redacted]	0	[redacted]	11.27	8.27	3.00	[redacted][2]
Step 4	[redacted]	41,685	[redacted]	11.27	8.27	3.00	[redacted][2]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.
The redacted values correspond to the following ranges:
[1] $255,000 to < $355,000
[2] $95,000 to < $115,000

6.46 Table 12 presents the discounted results of the economic analysis (as presented in the PSCR), which were based on the EU-IGFD Registry outcomes. The cost-effectiveness of mecasermin in the base case was estimated to be $95,000 to < $115,000 per QALY gained. The ESC noted that base case ICER presented in the submission was $95,000 to < $115,000 per QALY gained.

Table 12: Base case results of the modelled economic evaluation presented in the PSCR (discounted)

Model arm	Costs (AUD) ($)	QALYs	ICER: cost per QALY gained (AUD) ($)
EU-IGFD Registry (base-case analysis)			
Mecasermin	[redacted]	11.27	-
No treatment	$41,685	8.27	-
Incremental	[redacted]	3.00	[redacted][1]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; AUD = Australian Dollars; EU-IGFD = European Increlex® Growth Forum Database.
Source: Table 3-22, p123 of the submission
The redacted values correspond to the following range:
[1] $95,000 to < $115,000

6.47 The results of the key sensitivity analyses are summarised in Table 13. These are based on the model included in the submission without the corrections as presented in the PSCR. The model is most sensitive to the chosen option for extrapolation of utilities.

Table 13: Sensitivity analyses (submission model before corrections)

Analyses	Incremental cost (AUD) ($)	Incremental QALYs	ICER (AUD) ($)
Base case	[redacted]	**2.99**	[redacted][1]
Utility extrapolation, by HSDS (base case: Christensen et al 2007, midpoint extrapolation)			
Upper estimate (Option 2 in Figure 2 above)	[redacted]	1.97	[redacted][2]
Lower estimate (Option 3 in Figure 2 above)	[redacted]	4.00	[redacted][3]
BMI of the general population (base case: mean)			
+ 1 SD	[redacted]	2.99	[redacted][4]
- 1 SD	[redacted]	2.99	[redacted][3]
Rx discontinuation, Rx-related adverse events, mecasermin dosing and height velocity (Base-case: EU-IGFD Registry)			
Study 1419	[redacted]	2.41	[redacted][4]
Height velocity with mecasermin (base case: EU-IGFD Registry mean)			
Study 1419	[redacted]	2.43	[redacted][4]
Time Horizon (Base-case: 100 years)			
25 years	[redacted]	2.06	[redacted][2]
50 years	[redacted]	2.76	[redacted][1]
Utilities + Study 1419 data (base case: utilities Option1, EU-IGFD Registry data)			
Study 1419 data + Utilities (Option 2)	[redacted]	1.59	[redacted][5]
Study 1419 data + Utilities (Option 2) + 50-year TH	[redacted]	1.48	[redacted][5]
Discount rate for costs and benefits (base case: 5.0%)			
0.0%	[redacted]	13.06	[redacted][6]
3.5%	[redacted]	4.18	[redacted][7]

BMI = body mass index; HSDS = height standard deviation score; ICER = incremental cost-effectiveness ratio; SD = standard deviation; Rx = treatment; EU-IGFD = European Increlex® Growth Forum Database; TH = time horizon.
Source: Table 3-23, p124 of the submission; Economic model workbook.
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$135,000 to < $155,000*
[3] *$55,000 to < $75,000*
[4] *$115,000 to < $135,000*
[5] *$155,000 to < $255,000*
[6] *$25,000 to < $35,000*
[7] *$75,000 to < $95,000*

6.48 Despite the corrections to the model, the ESC considered there was high uncertainty in the base case proposed by the PSCR. The ESC considered that a sensitivity analysis was needed to address key uncertainties in utility values, and using Study 1419 data. The ESC noted that using Study 1419 as the base case (for treatment-related adverse events, mecasermin dosing, treatment discontinuation rate and height velocity) and the utilities Option 2 in Figure 2 above, the ICER was $155,000 to < $255,000 per QALY gained (in the new model).

6.49 The PBAC noted the discussion provided in the pre-PBAC response that height was used as the main outcome measure in the model because other potential parameters lack robustness for reliable modelling. The pre-PBAC response also acknowledged the uncertainty associated with extrapolation of utility estimates as applied in the model, although noted that in the absence of data specific to the SPIGFD population, Silva et

al. 2013[4], demonstrated that the effect of short stature and HRQoL is maintained in children.

Drug cost/patient/course

6.50 The drug cost per patient per year is presented in Table 14. The proposed price for mecasermin is $[redacted] per vial.

Table 14: Drug cost per patient for proposed drug

	Mecasermin Study dose and duration	**Mecasermin Model**	**Mecasermin Financial estimates**
Mean daily dose	Study 1419: 0.224 mg/kg EU-IGFD: 0.196mg/kg	0.196 mg/kg	0.196 mg/kg
Mean patient weight	Study 1419: 12.1 kg EU-IGFD: 22 kg	22 kg	22 kg
Mean duration	Study 1419: 6.0 years EU-IGFD: 3.7 years	Mean Rx duration (females starting Rx at age 2) = 12 [a] Mean Rx duration (males starting Rx at age 2) = 14 [b] Mean Rx duration (females starting Rx at age 5) = 9 [c] Mean Rx duration (males starting Rx at age 5) = 11 [d]	6 years
Total cost/patient ($)	NR	[redacted]	[redacted]
Cost/patient/year ($)	NR	[redacted]	[redacted]

NR = not reported; EU-IGFD = European Increlex® Growth Forum Database; mg = milligram; kg = kilogram.
[a] Source: Cell J14, Tx Cohorts Model, Economic model worksheet.
[b] Source: Cell FG14, Tx Cohorts Model, Economic model worksheet.
[c] Source: Cell BI14, Tx Cohorts Model, Economic model worksheet.
[d] Source: Cell HF14, Tx Cohorts Model, Economic model worksheet
Source: Section 3.8.1 and Table 4-6, pp122, 131 of the submission.

Estimated PBS usage & financial implications

6.51 This submission was considered by DUSC.

6.52 An epidemiological approach was used to estimate the financial impact of listing mecasermin on the PBS to treat SPIGFD.

6.53 In the absence of Australian prevalence data for SPIGFD, the submission used international sales and EU-IGFD Registry data for mecasermin to estimate the number of eligible patients.

6.54 Key inputs used in the financial estimates are shown in Table 15.

[4] Silva N, Bullinger M, Quitmann J, Ravens-Sieberer U, Rohenkohl A; QoLISSY Group. HRQoL of European children and adolescents with short stature as assessed with generic (KIDSCREEN) and chronic-generic (DISABKIDS) instruments. Expert Rev Pharmacoecon Outcomes Res. 2013 Dec;13(6):817-27.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population (0 to 100 years)	2022: 26,301,274 2023: 26,727,025 2024: 27,147,199 2025: 27,562,195 2026: 27,970,435 2027: 28,372,315	Australian Bureau of Statistics	
Eligible patients	0.000053%	Assumption based on sponsor's internal sales data from the top five European markets	This estimate is likely underestimated given the uncertainty in the numbers provided in the TGA application and the submission. This assumption was tested in the sensitivity analysis performed during the evaluation.
Uptake rate (ramp-up assumptions)	Yr 1: 0% Yr 2: 14% Yr 3: 29% Yr 4: 43% Yr 5: 57% Yr 6: 73%	Assumption based on sponsor's internal sales data from the top five European markets and cross-checked against European IGFD Registry data	Since mecasermin is the only treatment available for patients with SPIGFD, the uptake rates may be higher than those assumed by the submission. This assumption was tested in the sensitivity analysis performed during the evaluation. Also, it seems unlikely that there would be zero new patients in the first year of listing.
Treatment utilisation			
Patients initiating treatment	Yr 1: 0% Yr 2: 100% Yr 3: 50% Yr 4: 25% Yr 5: 25% Yr 6: 20%	Assumption	No new patients were assumed to initiate treatment in year 1 (2022) as only the grandfathered patients continuing treatment in year 1 were assumed. The submission did not justify this assumption.
Patients continuing treatment	Yr 1: 100% Yr 2: 0% Yr 3: 50% Yr 4: 75% Yr 5: 75% Yr 6: 80%	Assumption	The submission did not justify these assumptions.
Scripts dispensed per patient per year	9.823	Assumption based on Sales & EU-IGFD Registry Data	This seems reasonable. However, Study 1419 data were not utilised to estimate the number of scripts.
Costs			
Mecasermin	AEMP: $[redacted] per vial DPMQ: $[redacted] for S100 Private Hospital and $[redacted] for S100 Public Hospital and	Requested price	

Data	Value	Source	Comment
	Community Access		
Patient co-payment	$26.40 per script	Utilisation data for treatment available on the Growth Hormone program	
Costs to MBS	105: $45.00/ service 82200: $9.90/ service 66695: $30.50/ service 58300: $40.70/ service	105- Professional attendance by a specialist 82200- Professional attendance by a participating nurse practitioner 66695- Quantitation in blood or urine of hormones and hormone binding protein 58300- Bone age study	

SPIGFD = severe primary IGFD; AEMP = approved ex-manufacturer price; DPMQ = Dispensed Price for Maximum Quantity; TGA = Therapeutic Goods Administration; EU-IGFD = European Increlex® Growth Forum Database.
Source: Table compiled during the evaluation from Section 4 of the submission.

6.55 The financial estimates assumed a prevalence of 0.53 children with SPIGFD per million Australians, derived from sales data from five European countries (France, UK, Italy, Germany, Spain).

6.56 The estimated prevalence of SPIGFD in Australia is uncertain for the following reasons:

- The actual number of patients with SPIGFD is unknown in Australia. As per the paediatric endocrinologist advice included in the submission, approximately 50 people were expected to be living with SPIGFD Australia wide, whereas the financial estimates assumed only 4 to 15 patients treated with mecasermin (Table 16).
- The exact number of children affected with Laron syndrome, a typical representation of patients with growth hormone insensitivity disorder, is unclear. However, it was estimated that there were about 500 patients with Laron syndrome worldwide (Laron 20155). Although this number is unverified, Australian patients likely represent a small fraction of the global population. The paediatric endocrinologist estimated approximately 25-50% of SPIGFD patients would have Laron Syndrome.
- The TGA application for the orphan drug designation for mecasermin estimated a prevalence of 134 children with SPIGFD in Australia (consistent with the TGA indication), substantially greater than assumed in the submission.
- It was difficult to ascertain the accuracy of prevalence estimates given the uncertainty in the numbers provided in the TGA application and the submission.

6.57 Table 16 presents the estimated financial implications for listing mecasermin for SPIGFD patients.

[5] Laron Z. Lessons from 50 years of study of Laron syndrome. Endocrine Practice. 2015 Dec 1;21(12):1395-402.

Table 16: Estimated use and financial implications

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026	Year 6 2027
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of mecasermin						
Cost to PBS/RPBS less co-payments	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net financial implications						
Net cost to PBS/RPBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to MBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total cost to the government	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; MBS = Medicare Benefits Schedule.
Source: Tables 4-13, p136 of the submission.
The redacted values correspond to the following ranges:
[1] *<500*
[2] *$0 to < $10 million*

6.58 The total cost to the health budget (R/PBS and MBS) of listing mecasermin was estimated to be $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing.

6.59 Mecasermin treatment is currently being offered to < 500 patients in Australia on compassionate grounds at no cost (< 500 patients are currently receiving treatment, and < 500 is yet to initiate). A total of < 500 grandfathered patients continuing treatment for six years were added to the financial estimates. This estimate is reasonable given that mecasermin was TGA registered in 2019, and the patients can receive mecasermin until age 18. Therefore, grandfathered patients would meet the eligibility criteria for the PBS restriction despite the prior mecasermin treatment.

6.60 The net cost to the R/PBS may be underestimated because of the uncertainty in the patient numbers (< 500 patients in year 1 increasing to < 500 in year 6). In particular, the TGA application estimated substantially more patients with SPIGFD (N=134) and thus eligible for mecasermin treatment. There is also a potential for mecasermin use in patients with less severe forms of GH failure who are resistant to GH treatment. These patients would not be eligible based on the proposed PBS criteria.

6.61 The financial impact estimates were most sensitive to the assumptions regarding the prevalence estimates and uptake (Table 17). Increasing the disease prevalence to 1 and 2 per million increased the total cost of mecasermin listing to the health budget by 44% ($0 to < $10 million total costs over six years) and 136% ($0 to < $10 million total costs over six years), respectively. Prevalence estimates based on mecasermin sales from France also led to an increase of 82% ($0 to < $10 million total costs over six years). Increasing the uptake assumptions by 50% and 100% substantially increased the total cost to the health budget to $0 to < $10 million (+31%) and $0 to < $10 million (+110%) respectively.

Table 17: Sensitivity analyses: Net Cost to PBS at public price

	Prevalence per million	2022[a] ($)	2023 ($)	2024 ($)	2025 ($)	2026 ($)	2027 ($)
Prevalence estimated from sales data in top 5 European countries (France, UK, Italy, Germany, Spain)							
EU5-average number of patients assumed from second year onwards	0.53	[redacted][a, 1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalence estimated from EU-IGFD Registry (registry participants only in France, UK, Italy, Germany, Spain)							
EU-IGFD ramp up over 6 years	0.28	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
EU-IGFD average number of patients assumed from second year onwards	0.28	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Utilisation estimated from mecasermin sales in France [b]							
Prevalence based on sales data from France (and 100% uptake)	0.87	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimates based on assumed prevalence [c]							
Possible impact of increased prevalence (with base case uptake assumptions)	1.00	[redacted][a, 1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	2.00	[redacted][a, 1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimates based on different uptake rates [d]							
Base-case	Market uptake, %	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
50% uptake		[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
100% uptake		[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimates based on weighted mean weight from the EU-IGFD registry							
Weighted mean weight from years 1-10[f]		[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

GF = grandfathered; pts = patients; m = million, Rx=treatment.

[a] The ramp-up assumption for the first year of mecasermin listing (2022) was considered as zero as it accounted for patients currently receiving mecasermin on compassionate grounds. The submission did not justify this assumption.

[b] Calculated by dividing the sum of values in cells D18 to H18 by sum of D34 to H34 in the Sales & Registry Data worksheet, Financial workbook.

[c] In the sales & Registry data worksheet of the financials workbook, values in cells D57 and D58 were changed to estimate the impact of increased prevalence.

[d] The ramp-up assumptions were calculated by changing the values in cells F32 to J32 in the '2b.Patients- prevalent worksheet', Financials workbook.

[e] Calculated by changing mean weight (12.1kg; cell F169), mean daily dose (0.224mg/kg; cell F172) and mean treatment duration (6 years; cell F170) in the worksheet- 2e. Scripts- Market, Financial workbook. The resulting decrease in number of scripts per year was added to cells O117 to O119 in the 3a.Scripts-proposed worksheet of the Financials workbook.

[f] The weighted mean weight (33.5kg) was calculated by averaging the yearly weight of mecasermin treated patients in the EU-IGFD registry (Source: Table 14.3.26 - Evolution of weight (kg), EU-IGFD CSR). The resulting increase in number of scripts per year was added to cells O117 to O119 in the 3a.Scripts-proposed worksheet of the Financials workbook.

Source: Table 4-14, p137 of the submission; Worksheet sensitivity analysis, financials workbook.

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

[2] < 500

6.62 The PBAC noted that the DUSC considered the submission's estimates to be possibly underestimated, and had noted concerns about the estimated number of patients and the estimated utilisation per patient (Mecasermin DUSC Advice, November 2021 PBAC Meeting, p2 and p7).

6.63 The PBAC noted that Orphanet[6] estimates the prevalence of Laron syndrome to be 1-9 per 1,000,000, corresponding to approximately 25 - 225 cases in Australia.

Quality Use of Medicines

6.64 The submission did not provide any information on the quality use of medicines.

6.65 Information for prescribers and patient materials should be provided since mecasermin is a highly specialised medicine in a vulnerable population.

6.66 Education and training should include information regarding administration, including aseptic technique and measurement and administration, storage of the medicine and management of adverse events such as hypoglycaemia and lipohypertrophy.

Financial Management – Risk Sharing Arrangements

6.67 None proposed.

For more detail on PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend mecasermin 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 (SPIGFD). The PBAC considered the proposed PBS criteria inadequately defined the appropriate patient population. The PBAC considered that the incremental cost effectiveness ratio was high and uncertain at the proposed price, and that further validation of the estimated utilisation was required.

7.2 The PBAC noted there are currently no therapies available for SPIGFD, and that long term treatment with mecasermin may result in benefits beyond improved growth, including potentially improved neurodevelopmental function.

7.3 The PBAC considered that the proposed PBS criteria were inadequate to ensure that treatment is restricted to the appropriate patient population, especially given the potential for inappropriate use of mecasermin. The PBAC noted that the proposed PBS criteria did not reflect the clinical management algorithm presented in the submission with respect to screening patients on the basis of circulating levels of growth hormone binding protein (GHBP), IGF-1 generation tests and mutation analysis (see paragraph 4.9). The PBAC advised that further input was required to define the appropriate eligibility and continuation criteria, and considered that advice from Australian clinical experts, potentially through the Australasian Paediatric Endocrine Group (APEG), should be incorporated within any resubmission.

[6] https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=633

7.4 In addition to the discussion in paragraph 7.3, the PBAC provided the following specific advice regarding the restriction:

- A precise definition of GH sufficiency and adequate response to treatment was required;
- There should be documented confirmation of the diagnosis of severe IGF-1 deficiency at initiation of treatment, which may include confirmation of mutation in the growth hormone/IGF signalling pathway consistent with severe IGF-1 deficiency, in line with guidance in the PI.
- The criteria "Must not have fusion of epiphyses" should be stated in both the initiation and continuation restrictions.
- For continuing therapy, there should be a requirement for treatment to cease if a minimum increase in height velocity is not met (i.e. a stopping rule).

7.5 The PBAC considered the nominated comparator, no treatment, was appropriate.

7.6 The PBAC noted that the evidence presented in the submission included one head-to-head trial comparing mecasermin to no treatment (Trial MS301) and three single-arm studies. Trial MS301 was a randomised controlled, open-label trial with 137 participants and a study duration of one year. The PBAC noted first-year height velocities in Trial MS301 were increased for the mecasermin 80 µg/kg twice-daily and 120 µg/kg twice-daily groups compared with the untreated group (increase of 1.79 and 2.58 cm/year, respectively, both p<0001, see paragraph 6.12). The PBAC noted that higher rates of adverse events classified as 'metabolism and nutrition disorders', 'general disorders and administration site conditions', 'gastrointestinal disorders' and 'nervous system disorders' were observed in mecasermin-treated patients compared to the untreated group in Trial MS301 (see paragraph 6.22).

7.7 The PBAC considered that the submission's claim of superior comparative effectiveness was reasonable on the basis of improved height outcomes. The PBAC considered that mecasermin has inferior safety when compared with no treatment based on Trial MS301. The PBAC noted the most frequently reported adverse events included hypoglycaemia, headache, tonsil enlargement and vomiting (Midyett 2010, p616). The PBAC also noted the potential neoplasia risk described in the TGA product information.

7.8 Regarding the economic analysis, the PBAC noted the model was designed to track the height, height standard deviation score (HSDS), quality of life, and cost associated with either mecasermin or no treatment. Growth for patients not on treatment was assumed to follow that reported in Laron et al. (1993), according to their age and sex. Patients on mecasermin treatment were assumed to gain height according to the observations from the EU-IGFD registry. The PBAC acknowledged that limited clinical data are available to populate the model, and that this reflected SPIGFD being a rare condition. The PBAC noted that the modelled relative treatment effect was based on a naïve comparison of single arm studies and considered that this approach

was associated with substantial uncertainty. The results from Trial MS301 which provided a within-study comparison of mecasermin versus no treatment in a randomised design were not included in the economic model, however, the trial only provided results over a period of one year.

7.9 The PBAC noted the sensitivity analyses revealed large variation in the estimates of cost effectiveness (see Table 13), and that the incremental cost effectiveness ratio (ICER) for some of the sensitivity analyses exceeded $155,000 to < $255,000/QALY gained compared with $95,000 to < $115,000/QALY gained in the base case analysis. Overall, the PBAC considered that the ICER was unacceptably high and uncertain. The PBAC considered a price reduction would be required for mecasermin to be considered cost-effective.

7.10 The PBAC noted the submission's estimate of the number of patients to be treated with mecasermin of 4-15 is less than 15% of the estimated eligible patient population (134 patients in 2017) based on epidemiological estimates discussed in the TGA submission. The PBAC considered that further validation of the estimated utilisation is required, and any revisions to the restriction criteria as outline in paragraphs 7.3 and 7.4 should be accounted for.

7.11 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for mecasermin using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Patient population: Revised eligibility and continuation PBS criteria as outlined in paragraphs 7.3-7.4.
- A price reduction to increase the certainty that mecasermin is cost-effective (see paragraph 7.9).
- Financial estimates: Validation and/or revision of the estimated utilisation (see paragraph 7.10), and revised financial estimates incorporating the lower price for mecasermin.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Ipsen thanks the PBAC for their recognition of the unmet need in patients with SPIGFD, and look forward to further working with the committee in order to reach an outcome for children with this rare condition.