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

1 Purpose of Submission

1.1 The early re-entry resubmission sought to list mecasermin with a Section 100 Growth Hormone (GH) Program listing 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).

1.2 The resubmission sought to address the key matters of concern raised by the PBAC at the November 2021 meeting (Table 1).

Table 1: Summary of key matters to be addressed

Matter of concern	Resubmission	Addressed?
Patient population: The PBAC considered that the proposed PBS criteria inadequately defined the appropriate patient population (see paragraphs 7.1, 7.3-7.4).	The resubmission retained the criteria considered at the November 2021 PBAC meeting.	Addressed through the input sought by the PBAC from the Australasian Paediatric Endocrine Group (APEG),
Cost-effectiveness: The PBAC considered that the ICER was unacceptably high and uncertain, and that a price reduction would be required for mecasermin to be considered cost-effective (see paragraphs 7.1, 7.8-7.9).	The resubmission requested the same price as the November 2021 submission.	No. The resubmission stated that a price reduction was not feasible.
Financial estimates: The PBAC considered that further validation of the estimated utilisation was required due to uncertainty of the estimates. The PBAC also noted that revised financial estimates should take account of any revisions to the restriction criteria (as informed by expert clinical advice) and should apply a lower price for mecasermin (see paragraphs 7.1, 7.10-7.11).	The resubmission estimated that 77 to 83 patients would be treated with mecasermin per year (as compared with 4 to 15 patients per year in the November 2021 submission). The estimated number of scripts per year was increased to 12 (compared with 10 in the November 2021 submission).	No new evidence or clinical rationale was provided for the revised estimates. The resubmission stated that certainty of overall PBS expenditure would be provided by the proposed risk sharing arrangement (RSA), as it would apply [redacted]% rebate above the cap threshold.

Source: Mecasermin Public Summary Document (PSD), November 2021 PBAC meeting and compiled by Secretariat.

2 Background

2.1 Mecasermin was 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).

2.2 This is the second PBAC consideration of mecasermin for growth failure caused by severe primary IGFD (SPIGFD). Mecasermin was previously considered for this indication by the PBAC at its November 2021 meeting.

2.3 The growth hormone (GH)–insulin-like growth factor (IGF)-1 axis is the principal endocrine mechanism regulating linear growth in children. Mecasermin is a recombinant DNA-derived human IGF-1, which acts as replacement therapy for IGF-1 in patients with SPIGFD and therefore stimulates body growth. As such, there is a potential risk of misuse of mecasermin outside its approved indications, similar to that of somatropin. The PBS provides subsidised access to growth hormone (somatropin) through the Section 100 Growth Hormone Program, as specified in the *National Health (Growth Hormone Program) Special Arrangement 2015*. The purpose of the Growth Hormone Special Arrangement is to ensure that an adequate supply of pharmaceutical benefits is available for patients who require treatment with growth hormone. Restrictions on the provision of this treatment mean that these pharmaceutical benefits can more conveniently or efficiently be supplied under a special arrangement.

2.4 The PBS utilisation of somatropin was considered by the PBAC in July 2021, informed by analysis performed by the Drug Utilisation Subcommittee (DUSC)[1].

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission requested listing in the Section 100 Growth Hormone Program. This differed from the previous submission, which had requested listing in the Section 100 Highly Specialised Drugs Program. The resubmission (p7) stated that listing of mecasermin through the Growth Hormone Program would support quality use of the medicine and mitigate the risk of diversion outside the approved indication.

3.2 In November 2021, the PBAC considered that the proposed PBS criteria inadequately defined the appropriate patient population (paragraphs 7.1, 7.3-7.4, mecasermin Public Summary Document [PSD], November 2021 PBAC meeting). For this resubmission, the PBAC sought input directly from the Australasian Paediatric

[1] July 2021 PBAC meeting – Consideration of the report of the Drug Utilisation Sub-Committee, see https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2021-07/consideration-of-dusc-report-07-2021.pdf, accessed 11 January 2022.

Endocrine Group (APEG) about possible treatment criteria for mecasermin. The APEG advice was incorporated into the proposed restriction by the Secretariat. Additional discussion in relation to the APEG advice is provided in paragraphs 3.4 to 3.8.

3.3 The requested PBS listing is reproduced below. New 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 GH Program $[redacted]	Increlex

Category / Program: Section 100-*Growth Hormone Program* ~~(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: ~~g~~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: *(i)* 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 *on CDC2000 charts* (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:
	Patient must have a bone age less than 13.5 years (in girls) or 15.5 years (in boys)
	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
	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)
	Treatment criteria:
	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).
	Prescribing Instructions: <u>Maximum quantity/amount of drug selection:</u> 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 twice daily); (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:
Patient must have a bone age less than 13.5 years (in girls) or 15.5 years (in boys)
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
AND
Clinical criteria: (Proposed continuation criteria)
The patient is showing catch-up for height standard deviation score against Laron syndrome (GHIS) growth charts (Growth Curves for Laron syndrome, Archives of Disease in Childhood 1993; 68: 768-770). *and* *growth velocity > 2cm per year over the last 6 month period* *or,* *has not been on the maximum dose for the preceding approval period*
Treatment criteria:
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: <u>Maximum quantity/amount of drug selection:</u> 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).

3.4 The APEG recommended the following additions to the restriction for initiation of treatment, which have been included by the Secretariat:

- Low growth velocity indicated by baseline height velocity less than the 25th percentile for bone age on the Centers for Disease Control and Prevention (CDC) 2000 (CDC2000) charts[2].
- Bone age less than 13.5 years in girls and 15.5 years in boys.

3.5 The APEG noted that based on the current state of knowledge about the condition, a significant number of patients will not have a demonstrable molecular defect because new ones are being regularly described. The APEG recommended that confirmation of mutation in the growth hormone/IGF signalling pathway could be recorded as optional evidence if available.

3.6 The APEG recommended that GH sufficiency or insensitivity should be demonstrated and defined as random or stimulated growth hormone level > 6.6 ug/L. The pre-PBAC response suggested the reciprocal of the existing PBS restriction criteria (i.e., > 3.3 ug/L, as GH deficiency is defined as stimulation test < 3.3 ug/L) could be used instead, or the wording requested in the resubmission which required the prescriber to demonstrate the condition was not caused by growth hormone deficiency with reference to the pathology provider's 'normal' reference ranges (see proposed listing above).

3.7 The APEG noted that continuation criteria cannot be judged with reference to normal growth standards such as CDC2000 and that raw growth velocity is imprecise across age groups. The APEG recommended that some marker of response is needed, and suggested an approach similar to that which is currently used for Turner syndrome (applying to somatropin). The proposed continuation criteria were:

- Treatment can continue if:

  Bone age less than 13.5 years in girls and 15.5 years in boys

  and

  showing catch-up for Ht SDS against Laron syndrome (GHIS) growth charts (Growth Curves for Laron syndrome, Archives of Disease in Childhood 1993; 68: 768-770).

  and

  growth velocity > 2cm per year over the last 6 month period

  or,

  has not been on the maximum dose for the preceding approval period (in which case the dose can be put up if considered appropriate by the prescriber, as per growth hormone).

[2] Clinical Growth Charts, available from https://www.cdc.gov/growthcharts/clinical_charts.htm

3.8 The APEG requested the PBAC consider a mechanism for special consideration of cases that do not fit standard criteria for mecasermin treatment.

3.9 The resubmission requested the same price as the previous submission. The requested ex-manufacturer price was $ per vial, corresponding to a DPMQ of $ for a maximum quantity of 4 vials supplied via the GH Program.

3.10 The proposed PBS restriction aligns with the TGA indication, which is for the long-term treatment of growth failure in children and adolescents from 2 to 18 years (inclusive) with severe primary insulin-like growth factor 1 deficiency (Primary IGFD), noting that this age group includes patients until their nineteenth birthday.

3.11 The resubmission (p12) reported that the sponsor currently supplies four Australian patients with compassionate access to mecasermin at no cost to the patients. The financial estimates included four grandfathered patients treated each year.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 The November 2021 consideration of mecasermin was based on one head-to-head trial comparing mecasermin to no treatment (Trial MS301) and three single-arm studies (Study 1419, EU-IGFD Registry, and Petriczko et al. 2019). No additional clinical data were presented in the resubmission.

4.4 The PBAC previously 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 (paragraph 7.7, mecasermin PSD, November 2021 PBAC meeting.

Economic analysis

4.5 In November 2021, the PBAC considered that the ICER was unacceptably high and uncertain, and that a price reduction would be required

4.6 The resubmission requested the same price as the November 2021 submission and stated that a price reduction was not feasible.

Drug cost/patient/year

4.7 The estimated drug cost per patient per year of mecasermin is $[redacted], based on the proposed price (DPMQ $[redacted] for 4 x 40 mg vials) and the average drug utilisation reported in the EU-IGFD registry (mean daily dose of 0.196 mg/kg, mean patient weight of 22 kg, 3.274 vials per month, equivalent to 9.823 scripts per year).

Estimated PBS utilisation and financial implications

4.8 The resubmission applied the estimated prevalence of SPIGFD as reported in the TGA submission, which lead to an estimated eligible population of 146 patients in year 1, increasing to 157 in year 6 due to population growth. In addition, the resubmission assumed that 50% of the eligible patient population would be treated with mecasermin. The resubmission estimated that 77 to 83 patients would be treated with mecasermin per year, which included 4 grandfathered patients (Table 2).

4.9 The resubmission assumed that 12 scripts would be dispensed per patient per year, which was higher than the assumption in the November 2021 submission (9.823, based on the utilisation observed in EU-IGFD Registry). The PBAC considered this was not justified. The PBAC considered that the utilisation assumptions corresponding to the EU-IGFD registry should be applied in the estimates, consistent with the November 2021 submission. After adjustment to reflect the drug utilisation in the EU-IGFD registry, the estimated net cost to health budget was $10 million to < $20 million over six years (Table 2), compared with $0 to < $10 million in the November 2021 submission.

Table 2: Estimated use and financial implications of mecasermin

	2022	2023	2024	2025	2026	2027
Resubmission estimates with adjustment to reflect the drug utilisation in the EU-IGFD registry (scripts per year)						
Eligible patients	[1]	[1]	[1]	[1]	[1]	[1]
Treated proportion	50%	50%	50%	50%	50%	50%
Eligible patients treated	[1]	[1]	[1]	[1]	[1]	[1]
Grandfathered patients	[1]	[1]	[1]	[1]	[1]	[1]
Treated Patients	[1]	[1]	[1]	[1]	[1]	[1]
Scripts per year	9.823	9.823	9.823	9.823	9.823	9.823
Total Scripts	[2]	[2]	[2]	[2]	[2]	[2]
Cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Less co-payments	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]
Net cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to MBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget over 6 years						$[4]
Resubmission estimates						
Treated Patients	[1]	[1]	[1]	[1]	[1]	[1]
Scripts per year	[1]	[1]	[1]	[1]	[1]	[1]
Total Scripts	[2]	[2]	[2]	[2]	[2]	[2]
Cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Less co-payments	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]
Net cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to MBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget over 6 years						$[4]
November 2021 submission						
Treated Patients	[1]	[1]	[1]	[1]	[1]	[1]
Scripts per year	9.823	9.823	9.823	9.823	9.823	9.823
Total Scripts	[1]	[1]	[1]	[1]	[1]	[1]
Cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Less co-payments	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]	-$[3]
Net cost to PBS/RPBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to MBS	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget	$[3]	$[3]	$[3]	$[3]	$[3]	$[3]
Net cost to health budget over 6 years						$[3]

MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Source: Compiled by Secretariat.
The redacted values correspond to the following ranges:
[1]< 500
[2]500 to < 5,000
[3]$0 to < $10 million
[4]$20 million to < $30 million

4.10 The assumed MBS item utilisation and associated fees are provided in Table 3. The assumptions are unchanged from the November 2021 submission however the resulting MBS cost estimates are higher in the resubmission due to the increased number of patients assumed in the resubmission (Table 2).

Table 3: MBS item utilisation assumptions

MBS item	MBS item descriptor	Services per patient per yr	Scheduled fee
105	Professional attendance by a specialist	3.00	$45.00
82200	Professional attendance by a participating nurse practitioner	3.00	$9.90
66695	Quantitation in blood or urine of hormones and hormone binding protein	1.00	$30.50
58300	Bone age study	0.75	$40.70

Source: Net Changes – MBS sheet in Increlex (mecasermin) Financial Implications model.

Financial Management – Risk Sharing Arrangements

4.11 The resubmission (p19) proposed annual caps on PBS expenditure and stated that the sponsor would rebate % of the overall expenditure above the capped amount. The PBAC considered that adjustment to the estimates was required (see paragraph 4.9).

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the listing of mecasermin on the basis that it be available on a Section 100 Growth Hormone (GH) Program listing 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). The PBAC was satisfied that mecasermin provides, for some patients, a significant improvement in efficacy, based on improved height outcomes, over the nominated comparator, no treatment. The PBAC considered that the expert advice provided by the Australasian Paediatric Endocrine Group (APEG) had resolved the majority of concerns raised at the November 2021 PBAC meeting, and the remaining concerns could be addressed with an appropriate risk sharing arrangement. The PBAC noted that additional communication with APEG will be required to finalise the restrictions.

5.2 The PBAC considered that mecasermin would address an unmet clinical need, as there are no other reimbursed or TGA registered options for this patient population.

5.3 The PBAC considered that the advice from APEG had addressed the PBAC's previous concern that the patient population had been inadequately defined in the proposed PBS criteria. The PBAC provided the following additional comments about the requested listing and restriction:

- The PBAC noted the advice from APEG that supported listing of mecasermin with PBS arrangements as for somatropin, including listing of mecasermin through the Section 100 Growth Hormone program and that prescribing should be restricted to paediatric endocrinologists or to a paediatrician in consultation with a paediatric endocrinologist.
- The PBAC had previously noted that confirmation of the diagnosis of severe insulin-like growth factor 1 deficiency may include confirmation of mutation in the growth hormone/IGF signalling pathway. The PBAC considered that this information should not be considered mandatory (see paragraph 3.5).

- The PBAC had previously considered that a precise definition of growth hormone sufficiency was required. The APEG recommended to use a threshold defined as random or stimulated growth hormone level of > 6.6 ug/L. The PBAC considered that the APEG threshold was most appropriate for defining the eligible patient population (see paragraph 3.6).
- The PBAC noted that patients should not be treated if the epiphyses are fused, because mecasermin would not improve growth in these patients.
- The PBAC considered that minor outstanding issues with the restriction should be resolved by discussion with APEG, in relation to diagnostic criteria and continuation rules.
- The PBAC noted that additional work will be required to finalise the restrictions before listing can proceed. Changes will be required to the Growth Hormone Program legislation to incorporate mecasermin, and corresponding amendments may be required to the Services Australia system to accommodate mecasermin.

5.4 The PBAC noted the request from APEG to consider a mechanism for special consideration (paragraph 3.8). The PBAC did not support the proposal for special consideration arrangements, and considered that normal processes should be followed by prescribers with respect to assessment of patient eligibility for mecasermin.

5.5 With regard to utilisation estimates, the PBAC noted that the resubmission had assumed that 12 scripts would be dispensed per patient per year, which was higher than the assumption in the November 2021 submission (9.823, based on the utilisation observed in EU-IGFD Registry). The PBAC considered this was not justified, given that the resubmission also claimed to apply the utilisation observed in the EU-IGFD Registry. The PBAC considered that the financial estimates should be revised as described in paragraph 4.9.

5.6 The PBAC considered that the expert advice from APEG provided greater certainty with respect to the proposed PBS population (see paragraphs 3.2 to 3.7) and that the cost-effectiveness of mecasermin would be acceptable at the proposed price with the additional amendments to the restriction and an appropriate risk sharing arrangement. The PBAC advised that a risk sharing arrangement with [redacted]% rebate above annual cap thresholds should be implemented in order to address its previous concerns about financial uncertainty.

5.7 The PBAC recommended that mecasermin should not be treated as interchangeable with any other drugs.

5.8 The PBAC advised that mecasermin is not suitable for prescribing by nurse practitioners.

5.9 The PBAC recommended that the Early Supply Rule should not apply.

5.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for mecasermin:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies. The PBAC considered this criteria was not met as the available evidence showed a clinically relevant but modest improvement in height outcomes;

b) The treatment is expected to address a high and urgent unmet clinical need.

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 To be finalised. Add new medicinal product as follows (indicative only):

MEDICINAL PRODUCT **medicinal product pack**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
MECASERMIN				
mecasermin solution for injection 40 mg in 4 mL vial, 1	1	1	5	Increlex
Restriction summary / Treatment of Concept: [New 1]				
	Category / Program: Section 100 Growth Hormone Program			
	Prescriber type: ☒ Medical Practitioners			
	Restriction type: ☒ Authority Required (In-writing only via post/HPOS upload)			
	NOTE: 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. 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			
	NOTE:			

	Transitioning from non-PBS to PBS-subsidised supply –– 'Grandfather' arrangements: Apply under the 'Initial treatment' listing once only. Interpret the eligibility criteria in the context of when the patient initiated non-PBS supply.
	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
	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: (i) age, (ii) gender
	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 on 2000 Centers for Disease Control growth charts (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
	AND
	Clinical criteria:
	The condition must not be caused by growth hormone deficiency.
	AND
	Clinical criteria:
	Patient must have a bone age of less than 13.5 years (females); or
	Patient must have a bone age of less than 15.5 years (males)
	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
	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)
	Treatment criteria:
	Must be treated by a paediatric endocrinologist; the authority application must be completed by this physician type; or
	Must be treated by a paediatrician who has consulted the above mentioned specialist type; the authority application must be 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).
	Prescribing 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 twice daily); (iii) the number of vials rounded to the nearest whole number, to provide sufficient drug quantity for 30 days of treatment per dispensing. Seek an increase in the maximum quantity stated in the listing. The PBS authority application administrator will approve a maximum quantity of vials in line with the following formula (based on the upper dose range of 0.12 mg/kg dosed twice daily, one vial containing 40 mg of drug and target supply duration of 30 days per dispensing); Number of vials equals 7.2 multiplied by weight (kg) divided by 40 For ease in reference, this equates to: Below 16 kg: up to 3 vials 16 to 22 kg: up to 4 vials 22 to 27 kg: up to 5 vials 27 to 33 kg: up to 6 vials 33 to 38 kg: up to 7 vials 38 to 44 kg: up to 8 vials Beyond 44 kg: refer to above formula
	Prescribing Instructions: Evidence to be provided in support of this authority application (1) Insulin-like growth factor-1 deficiency: State each of: (a) the patient's most recent basal IGF-1 level measured in ng/mL, (b) the measurement date in dd/mm/yy format, (c) the name of the pathology result provider. (2) Short stature: State the patient's height in centimetres at time of this authority application. (3) Normal growth hormone levels: State the patient's most recent growth hormone level measurement in mcg/L - this figure must be greater than 6.6 mcg/L.
	NOTE: The Centers for Disease Control and Prevention (US) publishes Clinical Growth Charts which this restriction refers to. The relevant growth charts can be found here: <Specific citation to be added>

Restriction summary / Treatment of Concept: [New 2]	
	Indication: Severe growth failure with primary insulin-like growth factor-1 deficiency
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have a bone age of less than 13.5 years (females); or
	Patient must have a bone age of less than 15.5 years (males)
	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 condition is responsive to this drug treatment as evidenced by each of: (i) patient is showing catch-up for height standard deviation score against Laron syndrome (growth hormone insensitivity syndrome) growth charts, (ii) patient has a growth velocity of greater than 2 cm per year (extrapolated for time on treatment) at the time of this continuing authority application. or
	The condition is yet to respond to this drug treatment only for the reason of suspected sub-optimal dosing
	Treatment criteria:
	Must be treated by a paediatric endocrinologist; the authority application must be completed by this physician type; or
	Must be treated by a paediatrician who has consulted the above mentioned specialist type; the authority application must be 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: <u>Maximum quantity/amount of drug selection:</u> 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 30 days treatment per dispensing. Seek an increase in the maximum quantity stated in the listing.

	The PBS authority application administrator will approve a maximum quantity of vials in line with the following formula (based on the upper dose range of 0.12 mg/kg dosed twice daily, one vial containing 40 mg of drug and target supply duration of 30 days per dispensing); Number of vials equals 7.2 multiplied by weight (kg) divided by 40 For ease in reference, this equates to: Below 16 kg: up to 3 vials 16 to 22 kg: up to 4 vials 22 to 27 kg: up to 5 vials 27 to 33 kg: up to 6 vials 33 to 38 kg: up to 7 vials 38 to 44 kg: up to 8 vials Beyond 44 kg: refer to above formula
	NOTE: Laron syndrome growth charts are those appearing in the following publication: Growth Curves for Laron syndrome, *Archives of Disease in Childhood* 1993; 68: 768-770 Document growth improvements in the patient's medical records.

These restrictions are subject to further review.

7 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.

8 Sponsor's Comment

Ipsen has been pleased to work with the PBAC to ensure patients with SPIGFD have access to treatment with mecasermin for this rare condition.