

5.12 SOMAPACITAN, Injection 5 mg in 1.5 mL pre-filled pen, Injection 10 mg in 1.5 mL pre-filled pen, Injection 15 mg in 1.5 mL pre-filled pen, Sogroya[®], Novo Nordisk Pharmaceuticals Pty Limited.

1 Purpose of submission

- 1.1 This Category 2 submission requested Section 100 (Growth Hormone Program) Authority Required (Written) listing for the treatment of paediatric patients with growth hormone deficiency (GHD).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus somatogon (primary comparator and base case) and somatropin (secondary comparator and included as a sensitivity analysis).
- 1.3 The key components of the clinical issue addressed by the submission is presented in Table 1.

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

Component	Description
Population	Paediatric patients with growth hormone deficiency
Intervention	Somapacitan prefilled pen 5 mg/1.5 mL, 10 mg/1.5 mL or 15 mg/1.5 mL; weekly dosing at 0.16mg/kg/week
Comparator	Primary: Somatogon; weekly dosing Secondary: Somatropin; daily dosing
Outcomes	Height velocity, height velocity SDS, change in height SDS from baseline, change in IGF-1 SDS from baseline, IGFBP-3 SDS, quality of life, safety
Clinical claim	Non-inferior effectiveness and safety compared with somatogon in paediatric GHD Non-inferior effectiveness and safety compared with somatropin in paediatric GHD

Source: Table 1.1., p.27 of the submission

GHD = growth hormone deficiency; IGF-1 = insulin growth factor-1; IGFBP-3 = insulin-like growth factor binding protein 3; SDS = standard deviation score

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under the Therapeutic Goods Administration (TGA)/Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process for “the replacement of endogenous growth hormone (GH) in paediatric patients with growth failure due to growth hormone deficiency (GHD)”. The submission stated that TGA listing is expected by 31 October 2023. At the time of the PBAC consideration the TGA Delegate’s view was available.

Somapacitan was previously registered on the Australian Register of Therapeutic Goods (ARTG) in February 2022 for “the replacement of endogenous GH in adults with GHD”.

Previous PBAC consideration

- 2.2 Somapacitan was recommended for listing on the PBS by the PBAC for the treatment of GHD in adults at the March 2022 PBAC meeting. At the time of the PBAC consideration of this submission, somapacitan was not listed on the PBS.
- 2.3 The PBAC previously considered somatrogen for the treatment of paediatric GHD, and this was recommended on the basis of a CMA versus once-daily somatropin (somatrogen, Public Summary Document [PSD], March 2022 PBAC meeting).

3 Requested listing

- 3.1 The submission requested PBS listing for three presentations (5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL) of somapacitan for the following forms of GHD:
- Short stature associated with biochemical GHD (SSABGHD)
 - Short stature slow growth (SSSG)
- 3.2 The abridged requested listing of somapacitan for the initial and continuing treatment of patients with SSABGHD is presented below. The submission also requested the following listings: grandfathering treatment of SSABGHD, the initial, continuing, and grandfathering treatment of SSSG, and the Recommencement of treatment, Recommencement of treatment as a reclassified patient, Change of drug, and Continuing treatment as a reclassified patient for SSABGHD and SSSG.

MEDICINAL PRODUCT medicinal product pack	DPMQ AEMP	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SOMAPACITAN					
Somapacitan prefilled pen(s), 5mg/ 1.5 ml	\$332.82 (\$66.56 per mg) \$312.50 (\$62.50 per mg)	1	1	5	Sogroya, Novo Nordisk Pharmaceuticals Pty Ltd.
Somapacitan prefilled pen(s), 10mg/ 1.5 ml	\$657.83 (\$65.78 per mg) \$625.01 (\$62.50 per mg)	1	1	5	Sogroya, Novo Nordisk Pharmaceuticals Pty Ltd.
Somapacitan prefilled pen(s), 15mg/ 1.5 ml	\$982.83 (\$65.52 per mg) \$937.51 (\$62.50 per mg)	1	1	5	Sogroya, Novo Nordisk Pharmaceuticals Pty Ltd.

Source: Table 1.6, p.37 of the submission

AEMP = approved ex-manufacturer price; DPMQ = dispensed price maximum quantity

Category / Program: S100 Growth Hormone Program
Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
Condition: Short stature associated with biochemical growth hormone deficiency
Treatment Phase: Initial treatment
Clinical criteria:
• Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to:

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○ 2 pharmacological growth hormone stimulation tests (e.g. arginine, clonidine, glucagon, insulin); OR ○ 1 pharmacological growth hormone stimulation test (e.g. arginine, clonidine, glucagon, insulin) and 1 physiological growth hormone stimulation test (e.g. sleep, exercise); OR ○ 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) with other evidence of growth hormone deficiency, including septo-optic dysplasia (absent corpus callosum and/or septum pellucidum), midline abnormality including optic nerve hypoplasia, cleft lip and palate, midfacial hypoplasia and central incisor, ectopic and/or absent posterior pituitary bright spot, absent empty sella syndrome, hypoplastic anterior pituitary gland and/or pituitary stalk/infundibulum, and genetically proven biochemical growth hormone deficiency either isolated or as part of hypopituitarism in association with pituitary deficits (ACTH, TSH, GnRH or vasopressin/ADH deficiency); OR ○ 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels; OR ○ 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGFBP-3 levels,
AND • Patient must have a current height at or below the 1st percentile for age and sex; OR • Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and a growth velocity below the 25th percentile for bone age and sex measured over a 12 month interval (or a 6 month interval for an older child); OR • Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and an annual growth velocity of 14 cm per year or less if the patient has a chronological age of 2 years or less; OR • Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and an annual growth velocity of 8 cm per year or less if the patient has a bone or chronological age of 2.5 years or less,
AND • Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes,
AND • Patient must not have an active tumour or evidence of tumour growth or activity,
AND • Patient must not have previously received treatment under the PBS S100 Growth Hormone Program,
AND • Patient must be male and must not have a bone age of 15.5 years or more; OR • Patient must be female and must not have a bone age of 13.5 years or more.
Treatment criteria: • Must be treated by a specialist or consultant physician in paediatric endocrinology; OR • Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology,
AND • Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time.

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Category / Program: S100 Growth Hormone Program
Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
Condition: Short stature associated with biochemical growth hormone deficiency
Treatment Phase: Continuing treatment
Clinical criteria:
• Patient must have achieved the 50th percentile growth velocity for bone age plus sex following the most recent supply; OR • Patient must have achieved an increase in height standard deviation score for chronological age plus sex following the most recent supply; OR • Patient must have achieved a minimum growth velocity of 4 cm per year following the most recent supply; OR • Patient must have achieved a mid-parental height standard deviation score following the most recent supply; OR • The treatment must have been administered at a dose that is lower than that recommended in the approved Product Information in the most recent supply, AND • Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes, AND • Patient must not have an active tumour or evidence of tumour growth or activity, AND • Patient must be male and must not have a bone age of 15.5 years or more; OR • Patient must be female and must not have a bone age of 13.5 years or more.
Treatment criteria:
• Patient must be undergoing continuing PBS-subsidised therapy with this drug - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) recommence treatment, (iv) reclassify the PBS indication. AND • Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time.

- 3.3 The proposed AEMP was higher than the proposed published AEMP for adult GHD of \$547.83 or \$54.78 per mg (somapacitan, PSD, March 2022 PBAC meeting).
- 3.4 Like somatrogen, the requested restriction for somatropin was based on patient bone age (≤ 15.5 years for boys and ≤ 13.5 years for girls), which was not the demographic of the clinical trials where patients were enrolled based on chronological age (ranged between 2.5 and 11 years). The PBAC previously considered that while there is limited data available for somatrogen use in patients less than three years and between 12 and 18 years, treatment should not be restricted by a minimum age criterion and that eligibility based on skeleton maturity was reasonable given the clinical need for a weekly GH therapy (paragraph 7.6, somatrogen, PSD, March 2022 PBAC meeting).
- 3.5 The PBAC previously considered that without an upper dose limit specified for the continuing treatment phase (as per the somatropin criteria), it is possible that patients could receive sub-optimal doses of somatrogen and stop PBS treatment without the opportunity to increase the dose (paragraph 3.6, somatrogen, PSD, March 2022 PBAC meeting). Nevertheless, ultimately this upper dose limit was not included in the somatrogen restriction because the PI for somatrogen does not specify any dosing with respect to body surface area – it states that there is no clinical trial experience with doses above 0.66 mg/kg/week. Similarly, the draft PI for somapacitan did not

specify a dose expressed in relation to body surface area – it provided a single dose recommendation of 0.16 mg/kg/week without any guidance to dose beyond this value. In this submission, an upper dose limit of 4.99 mg/m²/week somapacitan (calculated by multiplying the upper dose limit of somatropin by the equi-effective dose ratio of somapacitan and somatropin) was proposed, although this was not included in the requested restriction criteria. There were no provisions for dose increase in the included somapacitan trial protocols (for REAL-3 and REAL-4), though the draft PI for somapacitan stated that dosages should be adjusted based on response. In REAL-4 the maximum reported dose of somapacitan was 0.17 mg/kg/week, whereas in REAL-3 the maximum somapacitan dose ranged between 0.223 and 0.275 mg/kg/week. Furthermore, a maximum clinical dose of 8 mg/week (relative to a starting dose of 1.5 - 4 mg/week) has been reported for adults (paragraph 3.2, somapacitan, PSD, March 2022 PBAC meeting). To date, the TGA has not assessed somapacitan at doses beyond this value as safe and efficacious, nor has it assessed a dose expressed in body surface area for safety and efficacy. Both the Pre-Sub-Committee Response (PSCR) and the evaluation considered that it may be reasonable to not include an upper dose limit beyond 0.16 mg/kg/week for somapacitan to be consistent with the somatrogen listing.

- 3.6 The submission requested that patients be able to switch from somatropin or somatrogen to somapacitan ('Change of drug' listing, Attachment 2 to the submission). The somapacitan trials included in the submission enrolled only treatment naïve, pre-pubertal patients. REAL-3 did not allow for treatment switching between GH therapies, and in REAL-4, while there was cross-over in the extension period, the results of the extension period were unavailable, hence the evidence to support this requested listing was limited. The PBAC previously considered that the risk of quality use of medicine (QUM) issues due to treatment switching was low given these decisions are at the discretion of treating endocrinologists (paragraph 7.8, somapacitan, PSD, March 2022 PBAC meeting; paragraph 7.7, somatrogen, PSD, March 2022 PBAC meeting). The proposed restriction criteria did not allow for treatment switching in patients who have failed GH treatment.
- 3.7 The submission proposed a threshold for the biochemical GHD of peak serum growth hormone concentration of less than 10mU/L or less than or equal to 3.3 micrograms per litre in response to growth hormone stimulation tests, based on the somatrogen listing. However, a different biochemical threshold was used to define the inclusion criteria in pivotal clinical trial (REAL-3), i.e., peak growth hormone level of less than 7.0 ng/mL. The PSCR maintained that the difference between a 7.0 and 10.0 ng/mL peak GH threshold was unlikely to result in significant applicability issues, a viewpoint

that was supported by the evaluation based on Hughes¹ (2012), which reported patients with biochemical GHD had median peak GH levels of 1.9 ng/mL. The PSCR also argued that the possibility of the peak GH level being a treatment modifier in REAL-4 was also marginal ($p=0.0466$).

- 3.8 It is possible that patients will require two different pens to achieve the full dose, highlighting an important QUM issue, with respect to minimising the risk of over- or under-dosing and preventing injection site reactions. There may also be implications on quality of life (QoL) if patients need more than one injection in a single day. Pens that are discarded with remaining doses can also result in wastage and therefore have financial implications. For example, the 15 mg pen is limited to delivering a maximum dose of 8.0 mg per administration; a 55 kg patient would require 8.8 mg (55×0.16) weekly dosing. The PSCR acknowledged that patients with higher weight may require multiple injections, however claimed that a similar issue has been observed with somatogon and prescribers would educate patients about correct dosing in practice which would reduce QUM concerns.
- 3.9 The submission proposed that the appropriate amount of drug (maximum quantity in units) that facilitated approximately 13 weeks of treatment per dispensing should be prescribed with a maximum of 1 repeat for approximately 26 weeks of treatment, and this treatment period appeared to apply to all treatment phases. This differed to the somatogon restriction, which allowed a maximum of 16 weeks per prescription for Initial, Recommencement or Recommencement as a reclassified patient, and 13 weeks for all other treatment phases. In the PSCR, the sponsor proposed an amendment to the Notes to allow for a 16-week treatment period for Initial, Recommencement or Recommencement as a reclassified patient treatment phases. The sponsor also proposed to update the prescribed maximum quantity (in terms of pens) to allow for 16 weeks of treatment.
- 3.10 The proposed maximum quantity of '1' unit was consistent with other listings on the Growth Hormone Program, but not reflective of the true quantity that would be prescribed to the patient. A maximum quantity of '1' has historically been listed where the dispensed amount is variable based on the patient's weight/body surface (BSA), there is a large range of potential patient weights/BSA, and where the intent is for an amount appropriate to the individual patient to be determined as part of the authority approval process such that for small patients, the authority application does not automatically default to the maximum quantity that is suitable for the large patient, as the treatment duration supplied would exceed the intended treatment duration for

¹ Hughes, I.P., et al. (2012), Growth hormone regimens in Australia: analysis of the first 3 years of treatment for idiopathic growth hormone deficiency and idiopathic short stature. *Clinical Endocrinology*, 77: 62-71. <https://doi.org/10.1111/j.1365-2265.2011.04230.x>

the small patient. The Secretariat advised that for each strength presentation, it is likely that a patient would need not more than 8 units per dispensing and therefore the declared maximum quantity could be specified as a number other than 1 unit. Prescribers are not obligated to prescribe the stated maximum quantity of units per prescription – they may prescribe a lesser quantity. To facilitate this, the Secretariat proposed a restriction requirement that the quantity sought in a prescription is to comply with that outlined in a 'Note' which gives guidance on the appropriate number of units per weight range (see Section 8 below).

- 3.11 The Secretariat determined the appropriate number of units for a given patient weight by considering:
- The recommended dose as per the product information (i.e., 0.16 mg/kg/week);
 - The targeted treatment duration (16 weeks in some treatment phases, 13 weeks in other treatment phases);
 - The 5 mg strength can deliver up to 2 mg per dose, the 10 mg strength can deliver up to 4 mg per dose, and the 15 mg strength can deliver up to 8 mg per dose;
 - The number of complete, full doses that can be extracted from a given strength (e.g., the 15 mg strength pen should be able to provide at least 2 doses for a large child, but could provide up to 7 complete doses for a small child);
 - Dependent on the number of complete, full doses that can be extracted from one pen, the multiple of that pen closest to the target duration (e.g. if one pen provides 6 complete doses, then 2 units will provide 12 doses, but 3 units will provide 18 doses – if the target is 16 weeks, the maximum quantity to be requested is to be 3 units as this quantity provides for at least 15 doses, but cannot provide exactly 15 doses);
 - The highest number of complete, full doses would be 7 given the shelf-life of 6 weeks (i.e., dosing would occur at days 0, 7, 14, 21, 28, 35 and 42 and then any remaining drug would need to be discarded)
 - Some patients/carers may not be prepared to adjust the dosing dial to completely exhaust the quantity of drug;
 - Only one particular strength would be prescribed at any given time, unless the patient was greater than 47 kg.

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

4 Population and disease

- 4.1 Paediatric GHD affects the bone, lipids, protein, and glucose metabolism, which results in abnormal growth height in children. Paediatric GHD may be congenital, acquired, or idiopathic. Causes for acquired GHD include brain tumours in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation,

and surgical intervention. The idiopathic origin of GHD is poorly understood but appears to be caused by multiple factors.

- 4.2 GH usually increases levels of the hormone insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) in the blood, which results in bone and height growth. Where paediatric GHD is diagnosed this does not occur and the recommended treatment is recombinant human growth hormone (rhGH) to achieve normalisation of height. GH therapy reduces body fat, reverses insulin insensitivity, and increases bone mineral mass.
- 4.3 Somapacitan is a novel, long-acting recombinant GH derivative that reversibly binds to serum albumin to prolong in vivo half-life of the drug, making it suitable for once-weekly subcutaneous dosing. Somapacitan has over 99% structural similarity to the naturally occurring GH, somatropin and is intended as a first-line (1L) therapy for paediatric GHD.

5 Comparator

- 5.1 The submission nominated somatogon (once-weekly dosing) as the main comparator and somatropin (once-daily dosing) as the secondary comparator. The main arguments provided in support of this nomination were that somatogon and somatropin are currently PBS-listed GH treatments for paediatric GHD. As somatogon is administered once weekly it was deemed most likely to be replaced in therapy. The ESC agreed that the nominated comparators were reasonable.

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 individuals (4) via the Consumer Comments facility on the PBS website. The comments described the potential benefit that once weekly, compared to daily, injections can have on quality of life.

Clinical trials

- 6.3 The submission was based on five head-to-head randomised controlled trials (RCT): REAL-3 (26-weeks, N=28) and REAL-4 (52-weeks, N=200) compared somapacitan to somatropin and Opko II (52-weeks, N=53), Opko III (52-weeks, N=224), and Opko JPN (52-weeks, N=44) compared somatogon to somatropin. No head-to-head RCTs were identified comparing somapacitan to somatogon, therefore the submission informed this comparison via a pairwise Bucher indirect treatment comparison (ITC) of the

pooled data from REAL-3 and REAL-4 versus (vs) Opko II and Opko III, using somatropin as the common comparator. Opko JPN was reasonably excluded from the meta-analysis/ITC due to the somatropin dose used being lower than in the other trials (0.025 vs 0.034 mg/kg/day, respectively). Results from the open-label extension (OLE) periods were reported in REAL-3 (three years), Opko II (three years), and Opko III (one year). Extension periods were noted in REAL-4 (three years) and Opko JPN (period not specified), but results were not available. Opko II (Study 4004), Opko III (Study 4006) and Opko JPN (Study 4009) have previously been considered by the PBAC in the PBAC's consideration for somatrogen in March 2022 (somatrogen, PSD, March 2022 PBAC meeting). The ESC considered that exclusion of the Opko JPN trial from the meta-analysis was reasonable.

- 6.4 The included trials all enrolled pre-pubertal patients aged between 2.5 and 11 years, while the proposed restriction requires patients have a bone age of up to 15.5 years for males and 13.5 years for females. There was limited evidence to support the use of somapacitan in patients older than 11 years and who are post-puberty, which was previously noted by the PBAC in its consideration for somatrogen (paragraph 7.6, somatrogen, PSD, March 2022 PBAC meeting).
- 6.5 The submission considered the ITC to be feasible given the comparability in baseline characteristics between REAL-3, REAL-4, Opko II, and Opko III trials. The evaluation considered this to be reasonable. There were slight differences in baseline clinical characteristics that potentially indicated that patients in REAL-4 and Opko III had less severe GHD compared to REAL-3 and Opko II as indicated by higher annualised HV SDS, height SDS, and peak GH levels at baseline. It was unclear if these differences were substantial enough to present transitivity issues. There were no notable differences in baseline characteristics in the common comparator (somatropin) arm across trials.
- 6.6 The evidence to support GH treatment switching is limited. Patients were GH treatment naïve in all the trials. REAL-3 did not allow for treatment switching, though REAL-4 allowed cross over to the somapacitan arm in its OLE period, but results were not available. Opko III allowed for patients to switch from somatropin to somatrogen in the OLE period, but implications from long-term results were unclear.
- 6.7 Provisions for somapacitan dose increases were not described in the pivotal trials. The mean somapacitan doses in REAL-4 were consistent around the recommended dose of 0.16 mg/kg/week, with a maximum dose of 0.17 mg/kg/week being reported. In REAL-3, the mean doses were more variable with doses increasing gradually from 0.146 to 0.157 mg/kg/week over the OLE period. However, the maximum doses in REAL-3 were considerably higher than the recommended dose, ranging between 0.223 and 0.275 mg/kg/week.
- 6.8 Details of the trials and the key publications 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
REAL 3 NCT02616562	REAL-3 Clinical study report Sävendahl L. Efficacy, Observer-Reported Outcomes, and Safety of Once-Weekly Somapacitan in Children with Growth Hormone Deficiency (GHD): 4-Year Results from the REAL 3 Trial	September 2018 Journal of Clinical Endocrinology Metabolism. 2022 Apr 19;107(5):1357-1367.
REAL 4 NCT03811535	REAL-4 clinical study report Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, Polak M, Bang RB, Böttcher V, Stagi S, Horikawa R. Weekly Somapacitan is Effective and Well Tolerated in Children with GH Deficiency: The Randomized Phase 3 REAL4 Trial. Zelinska N, Skorodok, J, Malievsky O, Iotova V, Rosenfeld R. G, Zadik Z, Vander S, Pastrak A. Long-Term Safety of a Once-Weekly Somatrogen (hGH-CTP): 4-Year Results of a phase 2 Extension Study in Children with Growth Hormone Deficiency	March 2022 Journal of Clinical Endocrinology Metabolism. 2022 Sep 5 January 2017
Opko II NCT01592500	Zelinska N, Iotova V, Skorodok J, Malievsky O, Peterkova V, Samsonova L, Rosenfeld RG, Zadik Z, Jaron-Mendelson M, Koren R, Amitzi L, Raduk D, HersHKovitz O, Hart G. Long-Acting C-Terminal Peptide-Modified hGH (MOD-4023): Results of a Safety and Dose-Finding Study in GHD Children.	Journal of Clinical Endocrinology Metabolism. 2017 May 1;102(5):1578-1587.
Opko III NCT02968004	Deal CL, Steelman J, Vlachopapadopoulou E, Stawerska R, Silverman LA, Phillip M, Kim HS, Ko C, Malievskiy O, Cara JF, Roland CL, Taylor CT, Valluri SR, Wajnrajch MP, Pastrak A, Miller BS. Efficacy and Safety of Weekly Somatrogen vs Daily Somatropin in Children With Growth Hormone Deficiency: A Phase 3 Study. Deal C, Pastrak A, Silverman L, Valluri SR, Wajnrajch MP, Cara JF. OR10-06 Somatrogen Growth Hormone in the Treatment of Paediatric Growth Hormone Deficiency: Results of the Pivotal Paediatric Phase 3 Clinical Trial.	April 2022 Journal of Clinical Endocrinology Metabolism. 2022 Jun 16;107(7):e2717-e2728. Journal of the Endocrine Society, Volume 4, Issue Supplement 1, April-May 2020
Opko JPN NCT03874013	Horikawa, R., Tanaka, T., Hasegawa, Y., Yorifuji, T., Ng, D., Rosenfeld, R. G., Hoshino, Y., Okayama, A., Shima, D., Gomez, R., Pastrak, A., & Castellanos, O. (2022). Efficacy and Safety of Once-Weekly Somatrogen Compared with Once-Daily Somatropin (Genotropin®) in Japanese Children with Paediatric Growth Hormone Deficiency: Results from a Randomized Phase 3 Study.	April 2022 Hormone research in paediatrics, 95(3), 275–285.

Source: Table 2.3, pp.52-3 of the submission

6.9 The key features of the included evidence that formed the basis of the ITC is summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in CMA
Somapacitan vs somatropin (common reference)						
REAL-3	28	R, DB, MC 6 mths + 3 yrs OLE	Low	Treatment naïve pre-pubertal children with GHD	Annualised HV	Not used
REAL-4	200	R, OL, MC 12 mths + 3 yrs OLE ^a	Low	Treatment naïve pre-pubertal children with GHD	Annualised HV	Used
Somatrogon vs somatropin (common reference)						
Opko II	53	R, OL, MC 12 mths + 3 yrs OLE	Low	Treatment naïve pre-pubertal children with GHD	Annualised HV	Not used
Opko III	224	R, OL, MC 12 mths + 12 mths OLE	Low	Treatment naïve pre-pubertal children with GHD	Annualised HV	Used
Opko JPN ^b	44	R, OL, MC 12 mths	Low	Treatment naïve Japanese pre-pubertal children with GHD	Annualised HV	Not used

Source: pp.55-9, Section 2.3 of the submission

CMA = cost minimisation approach; DB = double blind; GHD = growth hormone deficiency; HV = height velocity; MC = multi-centre; mths = months; OL = open label; OLE = open label extension; R = randomised; yr = year

^a OLE period in REAL-4 not available^b Not included in the ITC

Blue-highlight indicates trials previously considered by the PBAC

Comparative effectiveness

- 6.10 The primary efficacy endpoint was annualised height velocity (HV; cm/year) after 52-weeks in REAL-4, Opko II, Opko III, and Opko JPN. In REAL-3, this was a secondary outcome (the primary outcome in REAL-3 was annualised HV at 26 weeks). The results of the annualised HV at 52-weeks are presented in Table 4. Results of Opko JPN were not relied upon by the submission but have been presented for completeness.

Table 4: Results of annualised HV (cm/year) at 52-weeks across the trials: continuous data

Trial ID	Sompacitan 0.16 mg/kg/week	Somatropin 0.034 mg/kg/day	Somatrogon 0.66 mg/kg/week	Mean difference (95% CI), p-value ^a
	Annualised HV mean (SD) cm/year			
HV at 52W				
REAL-3 (n=14; 14)	11.70 (1.70 ^b)	9.90 (1.70 ^b)	-	1.80 (0.5, 3.1); 0.005
REAL-4 (n=132; 68)	11.20 (2.20 ^b)	11.70 (2.20 ^b)	-	-0.50 (-1.15, 0.15); 0.13
REAL-3 + REAL-4 (RE)	-	-	-	0.58 (-1.67, 2.83); 0.61; I ² =90%
REAL-3 + REAL-4 (FE)	-	-	-	-0.02 (-0.60, 0.55); 0.94; I ² =90%
Opko II (n=14; 11)	-	12.50 (2.10)	11.93 (3.50) ^c	-0.57 (-2.78, 1.64); 0.6 ^b
Opko III (n=109; 115)	-	9.78 (2.70 ^b)	10.10 (2.8 ^b)	0.32 (-0.39, 1.03); 0.38 ^{b d}
Opko JPN (n=22; 21)	-	7.87 ^e (NR)	9.65 ^e (NR)	1.79 (0.97, 2.61); NR
Opko II + Opko III (RE)	-	-	-	0.24 (-0.44, 0.92); 0.50; I ² =0%
Opko II + Opko III (FE)	-	-	-	0.24 (-0.44, 0.92); 0.50; I ² =0%
Indirect comparison				
REAL-3 + REAL-4 vs Opko II + Opko III (RE)	-	-	-	0.34 (-2.01, 2.69); 0.78
REAL-3 + REAL-4 vs Opko II + Opko III (FE)	-	-	-	-0.26 (-1.11, 0.63); 0.57
REAL-4 vs Opko II + Opko III	-	-	-	-0.74 (-1.68, 0.20); 0.12
REAL-4 vs Opko III	-	-	-	-0.82 (-1.78, 0.14); 0.10

Source: Tables 2.16-18, p.106; Table 2.58-9, pp.143-4 of the submission

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FE = fixed effects; HV = height velocity; ITC = indirect treatment comparison; MMRM = Mixed Model Repeated Measure; NR = not reported; RE = random effects; SD = standard deviation

Sample sizes for each timepoint read as: (n=number in intervention arm; number in comparator arm).

^a Adjusted mean change:

REAL-3: MMRM for repeated measurements, with treatment, age group, sex, region and sex by age group interaction as factors and height at baseline as a covariate, all nested within week as a factor;

REAL-4: ANCOVA with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height as covariates;

Opko III: ANCOVA model for stratification classes for treatment, age group, peak GH value during stimulation test, region and sex; baseline height SDS as a covariate

Opko JPN: ANCOVA model for treatment and sex as factors; peak GH value during stimulation test and baseline height SDS as covariates

^b not reported in CSR, calculated post hoc on RevMan 5.4.1

^c Results differed to Table 4, somatrogon PSD, March 2022 PBAC meeting. 11.93 cm/year as reported in Zelinska 2017 reported in submission but 11.4 reported in Table 4, somatrogon PSD, March 2022 PBAC meeting. Reason for discrepancy was unknown

^d Results differed to Table 4, somatrogon PSD, March 2022 PBAC meeting. 0.33 (95%CI -0.24, 0.89) reported in Deal 2022 and in Table 4, somatrogon PSD, March 2022 PBAC meeting. Reason for discrepancy was unknown.

^e Opko JPN calculated mean using the last squares mean. Somatropin dose in Opko JPN (0.025 mg/kg/day) was lower than other trials and was excluded from all meta-analyses and indirect comparisons

Bold indicates a statistically significant result (p<0.05)

Blue-shaded cells indicates values/text that have been previously considered by the PBAC

- 6.11 Based on the prespecified non-inferiority margin of -1.8 cm/year for annualised HV, which was previously accepted by the PBAC (paragraph 6.11, somatrogon, PSD, March 2022 PBAC meeting), the submission concluded that somatrogon was non-inferior to somatropin as the lower 95% confidence interval (CI) from the meta-analysis (-0.44) was greater than the non-inferiority margin. This was consistent with the PBAC's previous consideration of somatrogon (paragraph 7.4, somatrogon, PSD, March 2022 PBAC meeting).
- 6.12 For the comparison of somapacitan versus somatropin, both the individual trial results and the results from the meta-analysis from REAL-3 and REAL-4 demonstrated the

lower bound 95% CI for the mean difference in annualised HV fell within the prespecified -1.8 cm/year non-inferiority margin, supporting a claim of non-inferiority. REAL-3 reported that patients randomised to somapacitan had statistically significantly greater annualised HV at 52 weeks compared to patients randomised to somatropin (mean difference 1.80, 95% CI 0.5, 3.1, $p = 0.005$), though this was not observed in the larger REAL-4 trial, which could have contributed to the difference between the random effects (RE) and fixed-effects (FE) meta-analyses of the two somapacitan trials. Overall, the results from both REAL-3 and REAL-4 supported the submission's claim that somapacitan was non-inferior to somatropin. The TGA clinical evaluation report round 1 also indicated that for primary endpoint analyses, somapacitan led to similar improvements in growth as somatropin whilst the results for the secondary points including pharmacokinetic (PK) outcomes such as IGF-1 and IGFBP-3 SDS also supported the results of the primary endpoints.

- 6.13 The results of the ITC between somapacitan and somatropin based on the meta-analysis of REAL-3 and REAL-4 versus Opko II and Opko III, supported non-inferiority when the efficacy of somapacitan was informed by the FE model (lower 95% CI -1.11) but not the RE model (lower 95% CI -2.01). The point estimates suggested that annualised HV favoured somapacitan in the RE model but favoured somatropin in the FE model. There was high statistical heterogeneity between REAL-3 and REAL-4, that was not explored by the submission. The results of sensitivity analyses omitting REAL-3 from the ITC (i.e., REAL-4 only compared to Opko II and Opko III) supported non-inferiority.
- 6.14 The submission stated that the results from the RE model were attributable to the increased weight placed on REAL-3 (~50%) despite its smaller sample size, as well as the high statistical heterogeneity between REAL-3 and REAL-4, leading to a wide CI. While the limitations of the RE model were acknowledged, by relying on the FE model the heterogeneity observed between REAL-3 and REAL-4 was ignored, which can potentially lead to an overly precise summary estimate (i.e., a narrower CI) biasing the results in favour of a non-inferiority conclusion. The PBAC (p47 Guidelines for preparing a submission to the PBAC v5.0) has expressed a preference for using RE models in meta-analyses. The pre-PBAC response maintained that informing the ITC using the FE model was informative for decision making given the results from the RE model indicated high statistical heterogeneity between REAL-3 and REAL-4. The PSCR and the pre-PBAC response further claimed that FE models were informative for decision making as they assume a common effect size, resulting in less weighting placed on studies with smaller sample sizes. The evaluation considered that on balance, it was plausible that somapacitan was non-inferior in efficacy to somatropin, given that the PBAC has previously accepted that somatropin was non-inferior to somatropin, and somapacitan was also non-inferior to somatropin based on the direct trial results from REAL-3 and REAL-4. The ESC considered this was reasonable.

- 6.15 The results for somatropin varied between trials, with REAL-3 (9.90) and Opko III (9.78) reporting a lower mean annualised HV than REAL-4 (11.70) and Opko II (12.50) in patients randomised to somatropin. The cause of this difference was unclear, and the difference between trials could be considered substantial (e.g., the difference between the mean annualised HV in the somatropin arm of REAL-4 and REAL-3 was 1.8 cm/year, which was the same magnitude as the proposed non-inferiority margin, and the difference in Opko II and Opko III was even greater). It is possible that this difference contributed to the heterogeneity observed in REAL-3 and REAL-4, though the same degree of heterogeneity was not observed in the meta-analysis of Opko II and Opko III despite a similar difference in terms of mean annualised HV of the somatropin arm between the two trials. Overall, the variation in annualised HV seen with the common comparator increased the uncertainty of the ITC. The evaluation stated it was unclear if this represented a transitivity issue as the variation affected both the somapacitan versus somatropin trials and somatropin versus somatropin trials.
- 6.16 The submission considered that due to the greater bone age delay and lower peak GH levels and height SDS values in REAL-3 and REAL-4 compared to the Australian patient population, the treatment outcomes of somapacitan were expected to be conservative compared to clinical practice. However, the evaluation considered that this may not be a reasonable assertion as evidence to suggest this direction in treatment effect was uncertain and there were conflicting results in the literature.
- 6.17 For example, there was some evidence from REAL-4 subgroup data that peak GH level was a potential treatment modifier ($p=0.0466$) based on a test for interaction conducted during the evaluation. The treatment effect favoured somapacitan over somatropin (difference = 0.6, 95%CI -0.4, 1.6) in patients with higher peak GH levels (≥ 7 ng/ml), but favoured somatropin over somapacitan (difference = -0.7, 95%CI -1.5, 0.1) in patients with lower peak GH levels (< 7 ng/ml). This suggested that, compared to somatropin, somapacitan may be more effective in patients with less severe GHD, in which case the lower peak GH levels in REAL-3 and REAL-4 may have actually overestimated the efficacy of somapacitan compared to the expected efficacy in the proposed PBS population. Notably, in the Australian population, patients with biochemical GHD (BGHD, 1.9 ng/ml) had substantially lower peak GH levels compared to patients with SSSG (ISS, 9 ng/ml, and familial short stature [FSS], 6.9 ng/ml), and patients in REAL-3 (4.1 ng/ml) and REAL-4 (4.9 ng/ml). Assuming the treatment effect modification of peak GH levels exists, this would suggest that somapacitan is potentially less effective compared to somatropin in patients with BGHD compared to patients with SSSG (ISS and FSS). However, it is unclear whether the same relationship relative to somatropin would be observed.
- 6.18 In the literature, Yoon (2022) reported no significant difference in growth outcomes after one year between patients treated with somatropin with complete and partial GHD (i.e., more severe, and less severe GHD, respectively) and a significant difference

after two years. It was added that baseline height SDS was a significant negative predictor of growth response after one and two years in patients with more severe GHD, though, unlike REAL-4, peak GH level was not a significant predictor of growth outcomes in this study. Further highlighting the uncertainty in this relationship, other studies have reported a lower growth response in patients with less severe GHD compared to more severe GHD;^{2,3} no difference in growth response after one year;⁴ and that peak GH level was predictive of growth response.⁵ In addition, experts from the Growth Hormone Research Society (2019) recommended that patients with greater GHD severity, as evidenced by lower peak GH levels, lower IGF-1 levels, and clinical features, initiate GH treatment at lower doses, suggesting a higher sensitivity to treatment in these patients.⁶ Overall, it is unclear whether differences in GHD severity will have contributed to any differences in response to different treatments. As such, the claim that REAL-3 and REAL-4 represent conservative treatment estimates compared to the Australian population remains unclear.

- 6.19 Improvements in HV standard deviation score (SDS) and height SDS were consistent with improvements in annualised HV, and statistically significant differences for most comparisons between somapacitan vs somatropin and somapacitan vs somatrogon were not observed after 52 weeks.
- 6.20 Patient reported outcomes (TRIM-CGHD-O, TB-CGHD-O, and TB-CGHD-P)⁷ measuring the impact or burden of GH treatment based on REAL-3 and REAL-4 generally favoured somapacitan over somatropin. The submission reasonably considered QoL benefits of somatrogon compared to somapacitan to be applicable to somapacitan as both were once weekly GH treatments. The QoL benefits of somatrogon compared to somatropin were supported by the Quality of Life in Short Stature Youth (QoLISSY) questionnaire

² Isojima T, et al., (2017) The response to growth hormone treatment in prepubertal children with growth hormone deficiency in Japan: Comparing three consecutive years of treatment data of The Foundation for Growth Science in Japan between the 1990s and 2000s. *Endocr J.* 2017 Sep 30;64(9):851-858. doi: 10.1507/endocrj.EJ17-0063. Epub 2017 Jul 4. PMID: 28679975.

³ van den Broeck, J, et al. (2000), Growth Response to Recombinant Human Growth Hormone (GH) in Children with Idiopathic Growth Retardation by Level of Maximum GH Peak during GH Stimulation Tests. *Hormone Research* 1 July 2000; 53 (6): 267–273. <https://doi.org/10.1159/000053182>

⁴ Cardoso, D. F., et al., (2014). Comparison between the growth response to growth hormone (GH) therapy in children with partial GH insensitivity or mild GH deficiency. *Arquivos Brasileiros De Endocrinologia & Metabologia*, 58(1), 23–29. <https://doi.org/10.1590/0004-2730000002793>

⁵ Cole TJ, et al. (2004), Growth hormone (GH) provocation tests and the response to GH treatment in GH deficiency, *Archives of Disease in Childhood* 2004;89:1024-1027.

⁶ Collett-Solberg P.F., et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. *Horm Res Paediatr.* 2019;92(1):1-14. doi: 10.1159/000502231. Epub 2019 Sep 12. PMID: 31514194; PMCID: PMC6979443.

⁷ TRIM-CGHD-O: Treatment Related Impact Measure – Child-Growth Hormone Deficiency Observer, TB-CGHD-O: Treatment Burden Measure – Child-Growth Hormone Deficiency – Observer, and TB-CGHD-P: Treatment Burden Measure – Child-Growth Hormone Deficiency – Parent/Guardian.

(Opko III) and the Dyad Clinical outcomes Assessment (DCOA 1 and 2) questionnaire (NCT03831880 trial) from patients enrolled in Opko III. The PBAC previously considered that while the DCOA 1 questionnaire was validated for use among children with GHD, that using a subjective outcome in an unblinded trial was problematic. In addition, the PBAC previously noted there was no definition provided for non-inferiority, and no definition of a clinically significant difference (paragraph 6.15, somatrogen, PSD, March 2022 PBAC meeting).

Comparative harms

- 6.21 A summary of the results from the meta-analyses of adverse events (AE) from the included trials and the results of the ITC for AEs are presented in Table 5.

Table 5: Summary of meta-analysis and indirect comparison of key adverse events

Trial ID ^a	Somapacitan n (%)	Somatropin n (%)	Somatogron n (%)	RR (95% CI); p-value	RD (%) ^b (95% CI)
Any/all-cause AE					
REAL-3 + REAL-4 (RE)	107 (73.29)	55 (67.07)	-	1.04 (0.78, 1.40); 0.77 I ² =75%	6.21 (-5.89, 18.92)
REAL-3 + REAL-4 (FE)				1.13 (0.94, 1.35); 0.19 I ² =75%	
Opko II + Opko III (RE and FE)	-	105 (83.33)	105 (85.37)	1.03 (0.93, 1.14); 0.57 I ² =0%	2.03 (-7.18, 11.23)
ITC (RE) ^e	-	-	-	1.01 (0.74, 1.38); 0.95	-12.08
ITC (FE) ^e	-	-	-	1.1 (0.89, 1.35); 0.38	(-21.55, -2.33)
Serious AE					
REAL-3 + REAL-4 (RE)	7 (4.79)	3 (3.66)	-	1.38 (0.36, 5.36); 0.64 I ² =0%	1.14 (-5.86, 6.60)
REAL-3 + REAL-4 (FE)				1.40 (0.36, 5.39); 0.63 I ² =0%	
Opko II + Opko III (RE and FE)	-	2 (1.59)	3 (2.44)	1.58 (0.27, 9.29); 0.61 I ² =NE ^d	0.85 (-3.46, 5.54)
ITC (RE) ^e	-	-	-	0.87 (0.094, 8.087);0.91	2.36 (-2.69, 7.49)
ITC (FE) ^e	-	-	-	0.89 (0.096, 8.218);0.92	
Severe AE					
REAL-3 + REAL-4 (RE and FE)	4 (2.74)	1 (1.22)	-	2.06 (0.23, 18.08); 0.51 I ² =NE ^d	1.52 (-4.05, 5.83)
Opko II + Opko III (RE and FE)	-	6 (4.76)	9 (7.32)	1.58 (0.58, 4.30); 0.37 I ² =NE ^d	2.56 (-3.68, 9.19)
ITC (RE and FE) ^e	-	-	-	1.3 (0.12, 14.39); 0.83	-4.58 (-10.92, 0.63)
Treatment-related AEs					
REAL-3 + REAL-4 (RE and FE)	29 (19.86)	12 (14.63)	-	1.31 (0.71, 2.41);0.39 I ² =0%	5.23 (-5.61, 14.85)
Opko II (RE and FE)	-	0	5 (35.71)	8.80 (0.54, 143.81);0.13 I ² =NE ^d	35.71 (4.99, 61.70)
ITC (RE and FE) ^e	-	-	-	0.15 (0.01, 2.60); 0.19	-15.85 (-42.28, 5.02)

Source: Tables 2.32-47, pp.115-22; Figures 2.28-43, pp.136-41; Tables 2.63-66, pp.149-51 of the submission, Attachment 5 to the submission

AE = adverse events; CI = confidence interval; FE = fixed effects; ITC = indirect treatment comparison; n = number of participants reporting data; N = total participants in group; NE = not estimable; RD = risk difference; RE = random effects; RR = relative risk

^a Column read as: "Trial ID (n=number of patients in the intervention arm [i.e., somapacitan or somatogon]; number of patients in the comparator arm [i.e., somatropin])"

^b Risk difference calculated post hoc on StatsDirect during the evaluation

^c calculated post hoc on RevMan 5.4.1

^d Heterogeneity not assessed as meta-analysis was only include one study or one study did not report any events

^e For any/all-cause AEs, serious AEs, and severe AEs, REAL-3+REAL-4 vs Opko II + Opko III were compared. For treatment related AEs REAL-3+REAL-4 vs Opko II were compared (Opko III did not reported treatment related AEs).

6.22 The submission reported a significant difference in the relative risk (RR) of injection site pain frequency between somatogon and somatropin in Opko III (RR=1.56, 95% CI: 1.06, 2.31, p=0.025) and Opko JPN (RR=5.33, 95% CI: 1.81, 15.74, p=0.002) with fewer events in patients treated with somatropin. Comparatively, the incidence of injection site AE and injection site pain were low among patients treated with somapacitan or somatropin for both REAL-3 and REAL-4 with no statistically significant difference observed between treatments. No ITC results for injection site pain were provided. An ITC conducted during the evaluation comparing REAL-4 with Opko-III reported no statistically significant difference for injection site pain at 52 weeks (RR = 0.66, 95% CI 0.061, 7.201, p=7.335) between somapacitan and somatogon, though this was based on only three patients reporting any injection site pain (2/132 (1.5%))

in the somapacitan arm and 1/68 (1.5%) in the somatropin arm) in REAL-4, compared to 72 patients (43/109 (39.4%) treated with somatrogon and 29/115 (25.2%) treated with somatropin) in Opko III. The discrepancy in injection site pain reported in the somatropin arm between trials suggests that injection site pain may have been reported differently between trials and the results may not be comparable.

- 6.23 Overall, AEs were balanced between treatment arms across all trials. Differences observed across AEs did not lead to discontinuation in the trials. For example, in REAL-4, 27/132 (21%) patients in the somapacitan arm and 11/68 (16%) patients in the somatropin arm experienced treatment related AEs, but no patients discontinued treatment in this trial. Similarly, in Opko III, 43/109 (39%) patients in the somatrogon arm and 29/115 (25%) patients in the somatropin arm reported injection site pain but only 1/109 (1%) of patients discontinued in the somatrogon arm.
- 6.24 The development safety update report was included by the submission for the period 1 September 2021 to 31 August 2022 (no.11). To summarise, 580 subjects were exposed to somapacitan, and hypothyroidism was identified as an important risk. In REAL-4, hypothyroidism was reported more frequently in the somapacitan arm (6/132 [4.5%]) compared to somatropin arm (1/68 [1.5%]), and in REAL-3 hypothyroidism only occurred in one patient in the 0.04 mg/kg/week somapacitan arm.
- 6.25 The evaluation considered that a non-inferior safety claim compared to somatrogon and somatropin was reasonable. While a non-inferiority margin pertaining to safety was not presented, overall AEs were balanced between patients treated with somapacitan and patients treated with somatropin in REAL-3 and REAL-4. The point estimates for AEs in the ITC favoured somapacitan being associated with less treatment-related AEs and serious AEs compared to somatrogon, but the differences were not statistically significantly different. This was similarly concluded in the PBAC's previous consideration of somapacitan in adults (paragraph 7.4, somapacitan, PSD, March 2022 PBAC meeting).

Benefits/harms

- 6.26 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.27 The submission described somapacitan as non-inferior in terms of effectiveness compared to somatropin and somatrogon. The evaluation considered this claim was adequately supported for the comparison with somatropin based on direct evidence from REAL-3 and REAL-4.
- 6.28 The evaluation considered a claim of non-inferior effectiveness for somapacitan compared to somatrogon to be less clearly supported. Based on the ITC between somapacitan and somatrogon (with somatropin as the common comparator), non-inferiority between somapacitan and somatrogon could be concluded when results

from the FE model (for the meta-analysis of REAL-3 and REAL-4) were considered (mean difference -0.26, 95% CI -1.11, 0.63), however non-inferiority could not be inferred based on the results from RE model (mean difference 0.34, 95% CI -2.01, 2.69) as the lower 95% CI was less than the non-inferiority margin of -1.8 cm/year. While the limitations of the RE model are acknowledged, by relying on the FE model the heterogeneity observed between REAL-3 and REAL-4 is ignored which can potentially lead to an overly precise summary estimate (i.e., a narrower CI) which would bias the results in favour of a non-inferiority conclusion. Further, there was a substantial degree of variation in the annualised HV reported in the common comparator arm between each trial which increased the uncertainty of the results of the ITC.

- 6.29 Nonetheless, on balance, the ESC considered it was reasonable to conclude that somapacitan would be non-inferior in efficacy to somatrogen, given that the PBAC has previously accepted that somatrogen was non-inferior to somatropin, and somapacitan was also non-inferior to somatropin based on the direct trial results from REAL-3 and REAL-4.
- 6.30 The PBAC considered that the claim of non-inferior comparative effectiveness to somatropin and somatrogen was reasonable.
- 6.31 The PBAC considered that the claim of non-inferior comparative safety to somatropin and somatrogen was reasonable.

Economic analysis

- 6.32 The submission presented a CMA comparing somapacitan once-weekly with somatrogen once-weekly (base case) and somatropin once daily (sensitivity analysis). The key components and assumptions of the CMA are presented in Table 6.

Table 6: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the evidence presented in the submission, somapacitan OW is demonstrated to be non-inferior to somatrogen OW and somatropin OD with respect to changes in annualised height velocity at 52 weeks for the treatment of pGHD.
Therapeutic claim: safety	Based on the evidence presented in the submission, somapacitan OW is demonstrated to be non-inferior to somatrogen OW and somatropin OD with respect to all AEs at 52 weeks for the treatment of pGHD.
Evidence base	Base case analysis: Somapacitan versus somatrogen based on Bucher ITC of REAL-3 and REAL-4 vs Opko II and Opko III Sensitivity analysis: Somapacitan versus somatropin based on direct head-to-head comparison in REAL-3 and REAL-4
Equi-effective doses	Base-case analysis: 0.655 mg somatrogen = 0.157 ^a mg somapacitan (1 mg somatrogen = 0.240 mg somapacitan) Sensitivity analysis: 0.239 mg somatropin = 0.159 mg somapacitan (1 mg somatropin = 0.665 mg somapacitan)
Direct medicine costs	Weekly drug costs (effective AEMP): Base-case analysis Somapacitan = \$295.16 Somatrogen = \$295.16 Sensitivity analysis Somapacitan = \$298.13 Somatropin = \$298.13
Other costs or cost offsets	Not applicable

Source: Table 3.1, p.164 of the submission

AEMP = approved ex-manufacturer price; AE = adverse event; CSR = clinical study report; ITC = indirect treatment comparison; OD = once-daily; OW = once-weekly; pGHD = paediatric growth hormone deficiency; PSD = public summary document

^a Adjusted to account for differences between somatropin doses across REAL-4 and Opko III

- 6.33 The equi-effective doses were informed by the mean doses reported at 52 weeks in REAL-4 (0.159 mg/kg/week for somapacitan and 0.239 mg/kg/week for somatropin) and Opko III (0.655 mg/kg/week for somatrogen and 0.237 mg/kg/week for somatropin), which were used to inform the clinical claim of non-inferiority. The submission obtained the mean doses for Opko III from the somatrogen March 2022 PSD (Table 7, somatrogen, PSD, March 2022 PBAC meeting).
- 6.34 Given the 1% lower mean somatropin dose used in REAL-4 compared to Opko III (0.237 mg/kg/week vs 0.239 mg/kg/week), for the comparison with somatrogen the submission performed a 1% reduction to the mean somapacitan dose in REAL-4 (i.e., an adjustment of the dose from 0.159 to 0.157 mg/kg/week; see Table 7). The pre-PBAC response stated that a mean dose reduction of 1% for the somapacitan dose was appropriate for the purposes of the CMA, as its inclusion allowed for the calculation of an identical pack price for somapacitan in the CMA.

Table 7: Derivation of equi-effective dose based on mean doses in REAL-4 and Opko II

	Somapacitan	Somatropin	Somatrogon
REAL-4 (equi-effective doses in base case)	0.159 mg/kg/week	0.239 mg/kg/week	-
Opko III ^a	-	0.237 mg/kg/week	0.655 mg/kg/week
Equi-effective dose in base case	0.157 mg/kg/week ^b		0.655 mg/kg/week

Source: constructed during evaluation using information from p164-165 of the submission

^a Table 6, somatrogon, public summary document, March 2022 PBAC meeting

^b Mean somapacitan dose in REAL-4 × (mean somatropin dose in REAL-4 ÷ mean somatropin dose in Opko II)

6.35 The submission considered the weekly dose relativity to be:

- 1 mg somatrogon = 0.240 mg somapacitan
- 1 mg somatropin = 0.665 mg somapacitan

6.36 Even though the non-inferiority margin was met in the ITC using the FE model (or when excluding results from REAL-3), the point estimate of the treatment effect in the ITC trended in favour of somatrogon (see Table 4). Given that the dose of somapacitan can be adjusted based on response, it is possible that a dose higher than the equi-effective dose will be used in clinical practice to achieve a clinical outcome similar to somatrogon. The maximum doses observed in REAL-3 and REAL-4 (i.e., between 0.17 and 0.275 mg/kg/week) may suggest the upper dose limit for somapacitan. An increase in the somapacitan dose would decrease the cost per mg and therefore reduce the approved ex-manufacturer prices (AEMP). The PSCR argued that although point estimates may favour somatrogon, somapacitan and somatrogon were considered non-inferior to each other in terms of efficacy and safety based on Opko III and REAL-4. The PSCR further stated that in REAL-3, no patients exceeded the recommended dose of 0.16 mg/kg/week through 52 weeks, whilst in REAL-4, only a small proportion 3/132 (2.3%) of patients exceeded this recommended dose, which was possibly related to user errors or minor rounding errors when calculating the dose level, and that the mean dose observed in the trials would likely be reflective of clinical practice. The ESC agreed with the PSCR that the average dose of 0.16 mg/kg/week was reasonable.

6.37 The submission did not include additional costs or cost-offsets in the CMA stating that there were no notable differences associated with the administration between somapacitan and somatrogon/somatropin and somapacitan demonstrated non-inferior safety compared to somatrogon/somatropin. This approach was noted to be reasonable in the PBAC's consideration of somatrogon in paediatric GHD (paragraph 6.31, somatrogon, PSD, March 2022, PBAC meeting) and somapacitan in adult GHD (paragraph 6.26, somapacitan PSD, March 2022, PBAC meeting).

6.38 The results of the CMA as presented in the submission are presented in Table 8.

Table 8: Results of the cost-minimisation approach

Base case	Somapacitan OW	Somatrogon OW
Dose per kg per week	0.157 mg	0.655 mg
Dose per week ^a	4.72 mg	19.65 mg
Total medicine cost per week ^a	\$295.16 ^b	\$295.16
Cost per dose (AEMP)	\$62.50 per mg	\$15.02 per mg
Difference in cost per week	\$0	\$0
Sensitivity analysis	Somapacitan OW	Somatropin OD
Dose per kg per week	0.159 mg	0.239 mg
Dose per week ^a	4.77 mg	7.17 mg
Total medicine cost per week ^a	\$298.13 ^b	\$298.13 ^c
Cost per dose (AEMP)	\$62.50 per mg	\$41.58 per mg ^c
Difference in cost per week	\$0	\$0

Source: Table 3.3, p.167 of the submission

SA = sensitivity analysis; OD = once daily; OW = once weekly

^a Assumed a uniform average weight of 30 kg that stays consistent over time.^b Assumed equal to somatrogon and somatropin in the base case and sensitivity analysis, respectively.^c Does not incorporate price reductions as of 1 April 2023.

- 6.39 To calculate the dose (mg) per week, the submission used the equi-effective doses and applied an average patient weight of 30 kg. The submission noted that regardless of the assumed patient weight the resulting cost per mg was the same as only the total cost changed with patient weight. The ESC considered this was reasonable.
- 6.40 The cost per mg (AEMP) for somatrogon and somatropin were obtained from published PBS prices. The submission did not include the cost of the 5 mg presentation of somatropin in its calculation, noting that it was based on adult GHD, which is at a lower cost per mg than the 10 mg and 15 mg presentations (\$40.29 per mg vs \$41.58 per mg, respectively). Given that the restriction criteria for the 5 mg presentation did not preclude paediatric patients, the evaluation considered that exclusion from the CMA calculation may not be reasonable. Inclusion of the 5 mg somatropin presentation slightly decreased the somapacitan AEMP to \$61.85 per mg (compared with \$62.50, Table 8). The PSCR stated that the 5 mg presentation of somatropin was omitted from the CMA due to the inconsistent cost per milligram of the 5 mg presentation compared to the 10 mg and 15 mg presentations, i.e., \$40.29 for the 5 mg and \$41.58 for the 10 mg and the 15 mg presentations. This assumed that the cost per milligram for somatropin would be the same regardless of the presentation. However, the ESC considered that this may not be truly reflective of clinical practice as the 5 mg pen can be utilised in paediatric patients, and the 5 mg pen should be included in the analysis. In the pre-PBAC response the sponsor agreed to include the 5 mg presentation of somatropin in the CMA.

Drug cost/patient/year

- 6.41 The estimated cost per patient per year in the paediatric population is dependent on the patient weight. The cost per week, assuming a patient weight of 30 kg was

presented in the submission and additional analyses were performed during the evaluation using different patient weights (Table 9).

Table 9: Somapacitan and somatrogon patient weight, cost per mg, and cost per week

Base case (somapacitan vs somatrogon)	Somapacitan	Somatrogon
(0) Patient weight = 30 kg (base case)		
Dose per week ^a	4.72 mg	19.65 mg
Total medicine cost per week	\$295.16 ^b	\$295.16
Cost per dose (AEMP)	\$62.50 per mg	\$15.02 per mg
Difference in cost per week cf. base case	\$0.00	\$0.00
(1) Patient weight = 20 kg		
Dose per week ^a	3.15 mg	13.10 mg
Total medicine cost per week	\$196.77 ^b	\$196.77
Cost per dose (AEMP)	\$62.50 per mg	\$15.02 per mg
Difference in cost per week cf. base case	-\$98.39	-\$98.39
(2) Patient weight = 40 kg		
Dose per week ^a	6.30 mg	26.20 mg
Total medicine cost per week	\$393.55 ^b	\$393.55
Cost per dose (AEMP)	\$62.50 per mg	\$15.02 per mg
Difference in cost per week cf. base case	\$98.39	\$98.39

AEMP = approved ex-manufacturer price

^a Equi-effective doses: somapacitan = 0.157 mg/kg/week; somatrogon = 0.655 mg/kg/week. Assumed a uniform average weight of 30 kg (or specified weight in the sensitivity analysis i.e., 20 or 40 kg) that stays consistent over time.

^b Assumed equal to somatrogon.

- 6.42 Converting these weekly cost estimates into cost per year (i.e., multiplying the cost per week by 52) resulted in yearly costs of \$15,348 for a 30 kg child, \$10,232 for a 20 kg child, and \$20,464 for a 40 kg child. Only the base case (versus somatrogon) was presented. The sensitivity analysis (versus somatropin) resulted in a slightly higher cost compared to the base case for each respective weight.

Estimated PBS usage & financial implications

- 6.43 This submission was not considered by DUSC.
- 6.44 The submission used a market share approach to estimate the usage and financial impact of PBS listing somapacitan once weekly as an alternative to somatrogon in paediatric patients for the treatment of SSABGHD and SSSG.
- 6.45 The data sources used in the submission were the 10% PBS sample data, PBS utilisation statistics, REAL-4, and the Centre for Disease Control (CDC) growth charts. The market share approach assumed that 20% of the estimated patients in 2023 (Year 1) will receive once weekly GH therapy, and that use would be equally distributed between somapacitan and somatrogon (10% each) increasing annually thereafter to 65% (i.e., 32.5% each) in 2028 (Year 6). The market share of somatropin was not expected to change given somapacitan was expected to replace somatrogon as an alternative once-weekly GH treatment, thus was not included in the financial estimates, which was reasonable.

6.46 The approach taken to estimating the market share for somapacitan was reasonable, and key inputs are presented in Table 10.

Table 10: Key inputs for financial estimates

Data	Value applied and source							Comment	
Eligible population	The PBS 10% sample data for the number of SSABGHD and SSSG patients on GH therapy between January 2016 to September 2022 inclusive was linearly extrapolated to Year 1 (2023) to Year 6 (2028).							There was insufficient justification for linearly extrapolating patients. This issue was also noted for somatrogen in March 2022. The PBS 10% sample could not be validated but was likely comparable to the full PBS dataset thus was unlikely to significantly impact overall estimates (Table 9, somatrogen, PSD, March 2022 PBAC meeting).	
	Age (years)	Year							
		2016	2017	2018	2019	2020	2021		2022
	< 5	48	88	100	96	96	78		67
	5-9	418	376	372	353	381	412		462
	10-14	586	791	811	856	978	898		807
	Total	1,053	1,255	1,283	1,304	1,454	1,387		1,334
Source: PBS 10% sample data for the number of GH therapy for each month between January 2016 to September 2022 inclusive for the treatment of SSABGHD and SSSG (stratified by age group)									
Uptake rate	The estimated GH therapy market share for the treatment of SSABGHD and SSSG with PBS listing of somapacitan was based on crude estimates in lieu of more accurate evidence. The market share between somapacitan and somatrogen was assumed equal.							Uncertain. The submission did not provide appropriate justification for the assumed uptake rates. This issue was also noted for somatrogen in March 2022 (Table 9, somatrogen, PSD, March 2022 PBAC meeting). Somapacitan was estimated to increase overall patient co-payments compared to somatrogen, thus equal uptake rates may not be reasonable.	
	Market share/Year	Year 1 (2023)	Year 2 (2024)	Year 3 (2025)	Year 4 (2026)	Year 5 (2027)	Year 6 (2028)		
	Somapacitan	10.0%	20.0%	25.0%	27.5%	30.0%	32.5%		
	Somatrogen	10.0%	20.0%	25.0%	27.5%	30.0%	32.5%		
	Somatropin	80%	60%	50%	45%	40%	35%		
Source: Table 9, somatrogen, PSD, March 2022, PBAC meeting									
Average yearly dosing	The submission applied the mean yearly dose of 8.186 mg/kg (mean weekly dose at 52-weeks of 0.15742 mg/kg from REAL-4 multiplied by 52 weeks) to the assumed average weight of each age group. The average weight of patients <5 years was based on the CDC growth charts and for the 5-9- and 10-14-years age groups the average weights were obtained from the somatrogen March 2022 PSD. It was assumed that patients receive a full year of treatment.							CDC growth charts were reasonably generalisable to the Australian setting. As discussed in paragraph 6.36 the dose used in clinical practice may be higher than the equi-effective dose, which would increase the yearly doses. The average weight of the 10-14-year age group used in the submission was higher than that from the CDC data (44.5 versus 41kg, respectively).	
	Age (years)	Assumed average weight (kg)	Average yearly dose (mg/kg)		Average yearly dose (mg)				
	<5	12.2	8.186		100.1				
	5-9	24			196.5				
	10-14	44.5			364.3				
Source: REAL-4, Table 9, somatrogen, PSD, March 2022, PBAC meeting, and CDC growth charts for age-specific weights									

Data	Value applied and source		Comment
Distribution of somapacitan pens	Using the average yearly dose, the submission calculated the number of pens per year per presentation for each age group (i.e., average yearly dose divided by 5, 10, or 15 mg/1.5 ml presentations) and then weighted them by the estimated distribution of pens for each age group. The distribution of pens among the age groups was based on the Sponsor's internal forecasts and assumptions.		The submission claimed wastage was considered but it was unclear how this was accounted for in determining the pen distributions used. According to the REAL-4 pen selection guide and the average weight of each age group, it was possible that different presentations are prescribed, which was not explored in the submission.
	Age (years), average weight	Assumption	
	<5, 12.2 kg	100% receive 5 mg/1.5 ml pen = 20.02 pens	
	5-9, 24 kg	100% receive 10 mg/1.5 ml pen = 19.65 pens	
	10-14, 44.5 kg	20% receive 10 mg/1.5 ml pen = 36.43 pens 80% receive 15 mg/1.5 ml pen = 24.28 pens	
	Source: Table 9, REAL-4 CSR somapacitan pen injection selection guide, CDC growth charts, Sponsor internal estimates		
GH therapy costs and utilisation of GH therapy	Cost of GH therapies as subsidised by the PBS, and results from the CMA were used to inform the financial impact of somapacitan listing. The somapacitan and somatrogen AEMPs are presented below. To estimate the utilisation of GH therapy, the submission used the patient beneficiary category distribution for somatropin for the treatment of SSABGHD and SSSG on the PBS (Table 4.1.2, Attachment 4 to the commentary)		It is possible that the somapacitan dose used in clinical practice is higher than the equi-effective dose (see paragraph 6.36).
	Somapacitan	Somatrogen	
	5 mg/1.5 ml \$312.50	24 mg/1.2 ml \$360.50	
	10 mg/1.5 ml \$625.01	60 mg/1.2 ml \$901.25	
	15 mg/1.5 ml \$937.51		
	Source: PBS and CMA (Section 3)		

Source: Tables 4.4-9, pp.172-6; Table 4.11, p.177 of the submission

AEMP = approved ex-manufacturer price; CDC = Centre for Disease Control; CMA = cost minimisation analysis; GH = growth hormone; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; SSABGHD = Short stature associated with biochemical growth hormone deficiency; SSSG = short stature and slow growth

6.47 The estimated number of treated patients, scripts dispensed, and financial implications of listing once weekly somapacitan compared to somatrogen in paediatric patients for the treatment of SSABGHD and SSSG are presented in Table 11 and Table 12.

Table 11: Estimation of number of treated patients, prescriptions and the financial implications – somapacitan

	Variable	Method/Assumption	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population								
A1	<5 years	Linearly extrapolated to 2023-2028 from 2016-2022 data	1	1	1	1	1	1
A2	5-9 years		1	1	1	1	1	1
A3	10-14 years		2	2	2	2	2	2
A4	Total	A1 + A2 + A3	2	2	2	2	2	2
Estimated number of patients treated with somapacitan								
B	Estimated market share	Equal with somatrogen	10.0%	20.0%	25.0%	27.5%	30.0%	32.5%
C1	<5 years	A1 x B	1	1	1	1	1	1
C2	5-9 years	A2 x B	1	1	1	1	1	1
C3	10-14 years	A3 x B	1	1	1	1	1	1
Total somapacitan script numbers ^a								
F1	5 mg/1.5 ml	C1 x (100.1/5) x 100%	1	1	1	1	2	2
F2	10 mg/1.5 ml	C2 x (196.5/10) x 100% + C3 x (364.3/15) x 20%	2	2	2	2	3	3
F3	15 mg/1.5 ml	C3 x (364.3/15) x 80%	2	2	3	3	3	3

Source: Table 4.4 and Figure 4.1, p.172; Table 4.6, p.173; Tables 4.8-11, pp.176-7 of the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Distribution of pens was based on REAL-4 pen selection guide and internal sponsor estimates. The yearly dose for each age group was based on the mean yearly dose of 8.186 mg/kg and the average weight for each age group from CDC growth chart (<5 years = 12.2 kg; 5-9 years = 24 kg; and 10-14 years = 44.5 kg). See Table 10

The redacted values correspond to the following ranges:

¹ < 500² 500 to < 5,000³ 5,000 to < 10,000**Table 12: Financial implications of somapacitan to the PBS/RPBS**

	Year 1 (2023)	Year 2 (2024)	Year 3 (2025)	Year 4 (2026)	Year 5 (2027)	Year 6 (2028)
Estimated extent of use						
Number of patients treated ^a	1	1	1	1	1	2
Number of scripts dispensed ^b	2	3	3	4	4	4
Estimated financial implications of somapacitan – based on proposed DPMQ						
Cost to PBS/RPBS less co-payments	5	5	5	5	5	6
Estimated financial implications of somatrogen – based on published DPMQ ^c						
Cost to PBS/RPBS less co-payments	7	7	7	7	7	7
Net financial implications of somapacitan replacing somatrogen						
Net cost PBS / RPBS	7	7	7	7	7	7

Source: Table 4.19, p.181 of the submission

DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Sum of patients treated with somapacitan = C1 + C2 + C3 (Table 11)^b Sum of somapacitan scripts = F1 + F2 + F3 (Table 11)^c The approach used to estimate the market share and financial implications of somatrogen was identical to the approach used for somapacitan but for the doses and pens which were specific to somatrogen.

The redacted values correspond to the following ranges:

¹ < 500² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ \$0 to < \$10 million

⁶ \$10 million to < \$20 million

⁷ net cost saving

- 6.48 The submission estimated that somapacitan would result in a net savings in Year 1 and Year 6. The 'savings' estimated for somapacitan compared to somatrogon was a result of increased patient co-payments with somapacitan (due to more somapacitan pens being dispensed). The pre-PBAC response stated that as the financial estimates presented in the March 2022 submission for somatrogon claimed net savings and this submission also requested the same weekly cost as somatrogon, the proposed listing should be considered cost-neutral to the PBS. The ESC considered that there is no clear motivation to preferentially prescribe somapacitan over somatrogon (and therefore uptake rates in this submission may be overestimated), and that somapacitan should be cost neutral to somatrogon.
- 6.49 Sensitivity analyses around the financial estimates showed that changes in dollar terms was likely to be small, with no plausible scenario resulting in a net cost to the R/PBS. The pre-PBAC response presented an exploratory analysis of the net financial impact of assuming a 50% increase in the use of somatrogon in the weekly GH market, reducing the estimated use of somapacitan, and this analysis showed there would be a slightly smaller minor save to the R/PBS associated with PBS listing of somapacitan.
- 6.50 The sponsor noted that an Early Access Program is expected to be implemented in October 2023, but the number of patients expected to enrol is unknown. Thus, grandfathered patients were not included in the financial estimates. Assuming that only patients who were treated with somatropin or somatrogon on the PBS were enrolled in the Early Access Program, this may be reasonable. However, no details of the enrolment criteria for the program were provided.

Quality Use of Medicines

- 6.51 The submission did not outline QUM activities. The submission provided the most recent development safety update report for somapacitan that was described in paragraph 6.22. The submission also referenced potential QUM issues that were previously highlighted by the PBAC in the somatrogon and somapacitan submissions in March 2022. These related to treatment switching, concurrent use of GH therapies, and the possibility of requiring more than one somapacitan injection per week. It was unclear if the addition of a third exchangeable product would cause any additional risks for poor QUM.

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

7 PBAC outcome

- 7.1 The PBAC recommended the Section 100 Growth Hormone Program listing of somapacitan for the treatment of paediatric patients with growth hormone deficiency (GHD). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of somapacitan would be acceptable if it were cost-minimised to the lowest priced comparator of somatropin or somatrogen, for the same indication.
- 7.2 The PBAC advised that the equi-effective doses are:
- 1 mg of somatrogen is equivalent to 0.240 mg of somapacitan
 - 1 mg of somatropin is equivalent to 0.665 mg of somapacitan.
- 7.3 The PBAC noted that the consumer comments were supportive of making somapacitan available on the PBS, and that they stated that weekly injections have the potential to improve the quality of life for the paediatric population compared to the daily injections.
- 7.4 The PBAC noted that there was limited evidence to support the use of somapacitan in patients older than 11 years and those who are post-puberty. However, as with the somatrogen listing (paragraph 7.6, somatrogen, PSD, March 2022 PBAC meeting), the PBAC considered that treatment should not be restricted to a minimum age but rather, that eligibility based on bone age was reasonable.
- 7.5 The PBAC considered that the nominated main comparator somatrogen (once-weekly dosing) and the secondary comparator somatropin (once-daily dosing) were reasonable, with both somatrogen and somatropin currently PBS-listed for paediatric GHD.
- 7.6 The PBAC noted that the comparison of somapacitan and somatropin was based on two head-to-head randomised controlled trials (REAL-3 and REAL-4) and that these trials had a low risk of bias. The PBAC noted that the comparison of somapacitan and somatrogen was based on a pairwise Bucher indirect treatment comparison (ITC) of the pooled data from REAL-3 and REAL-4 versus two head-to-head RCTs comparing somatrogen to somatropin (Opko II, Opko III), with Opko JPN being reasonably excluded from the meta-analysis/ITC due to the somatropin dose being lower than the dose used in the other trials (0.025 mg vs 0.034 mg/kg/day, respectively).
- 7.7 The PBAC noted that, based on the results from REAL-3, at year 3, patients treated with somapacitan (0.16 mg/kg/week) had a similar change in height velocity standard deviation score (SDS) from baseline, as well as change in height SDS from baseline, compared to the daily somatropin injections (0.034 mg/kg/day). The PBAC further acknowledged that a comparable height velocity increase was observed for somapacitan and for somatropin in REAL-4 at 52 weeks. Based on the results from REAL-3 and REAL-4, the PBAC considered that the lower bound 95% CI for the mean

difference in annualised HV fell within the prespecified -1.8 cm/year non-inferiority margin, supporting the claim of non-inferiority.

- 7.8 The PBAC noted that the ITC of height velocity between somapacitan and somatrogen based on the meta-analysis of REAL-3 and REAL-4 versus Opko II and OpKo III, demonstrated non-inferiority based on the results of the fixed effects model (lower 95% CI -1.11) but not when the random effects model (lower 95% CI -2.01) was used. However, the PBAC considered somapacitan was likely to be non-inferior in efficacy to somatrogen given that somatrogen was considered non-inferior to somatropin, and that somapacitan was also non-inferior to somatropin based on the direct trial results from REAL-3 and REAL-4.
- 7.9 The PBAC noted that patient reported outcomes (TRIM-CGHD-O, TB-CGHD-O, and TB-CGHD-P) from REAL-3 and REAL-4 were similar between somapacitan and somatropin and considered that the quality of life benefits would likely be similar between the daily and weekly injectables.
- 7.10 The PBAC noted that there was a similar distribution of adverse events among the treatment groups in all trials, and there were no discernible variations in adverse events that resulted in discontinuation. The PBAC noted that for example, while 27/132 (21%) of patients in the somapacitan arm and 11/68 (16%) patients in the somatropin arm experienced treatment related AEs in REAL-4, there were no discontinuations in this trial. The PBAC considered that the claim of non-inferior safety compared to somatrogen and somatropin was reasonable
- 7.11 The PBAC noted that to account for a 1% lower mean somatropin dose used in REAL-4 (0.159 mg/kg/week for somapacitan and 0.239 mg/kg/week for somatropin) compared to Opko III (0.655 mg/kg/week for somatrogen and 0.237 mg/kg/week for somatropin), the submission reduced the mean somapacitan dose in REAL-4 by 1% (i.e., an adjustment of the dose from 0.159 to 0.157 mg/kg/week) in its calculation of the equi-effective doses. This resulted in the weekly dose relativity as 1 mg somatrogen (0.655 mg/kg/week) being equal to 0.240 mg of somapacitan (0.157 mg/kg/week) and 1 mg somatropin (0.239 mg/kg/week) being equivalent to 0.665 mg of somapacitan (0.159 mg/kg/week) respectively. The PBAC considered that the submission's approach was reasonable.
- 7.12 The PBAC considered that the 5 mg strength for somatropin should be included in the CMA.
- 7.13 The PBAC considered the market share approach used to derive the utilisation and financial estimates and the structure of the estimates model were reliable for decision-making.
- 7.14 The PBAC considered it was reasonable for the somapacitan's PBS eligibility criteria to be identical to the listings for somatrogen, for initial, continuing, grandfathering treatment, as well as recommencement of treatment, recommencement of treatment

as a reclassified patient, change of drug and continuing treatment as a reclassified patient.

- 7.15 The PBAC considered that specification of a minimum age restriction in the requested restriction for somapacitan was not required, and that this would be consistent with the listing for somatrogen.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because somapacitan is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over somatropin and somatrogen, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new medicinal product (somapacitan) as follows:

Category / Program: Section 100 – Growth Hormone Program					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SOMAPACITAN					
somapacitan 5 mg/1.5 mL injection, 1.5 mL pen device	NEW 1 MP	8	8	1	Sogroya
somapacitan 10 mg/1.5 mL injection, 1.5 mL pen device	NEW 2 MP	8	8	1	Sogroya
somapacitan 15 mg/1.5 mL injection, 1.5 mL pen device	NEW 3 MP	8	8	1	Sogroya
Common Administrative Advice that applies to each restriction summary within this prescribing rule:					
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. 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 authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)					

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	Alternatively, applications for authority to prescribe can 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
	Administrative Advice: An appropriate amount of drug (maximum quantity in units) for this treatment phase listing (approximately 16 weeks of treatment, which equates to at least 15 doses) per dispensing for various patient weight ranges, is outlined below: 5 mg strength presentation: Below 11 kg: up to 5 units 11 to 13 kg: up to 8 units 10 mg strength presentation: Below 13 kg: up to 3 units 13 to 16 kg: up to 4 units 16 to 21 kg: up to 5 units 21 to 25 kg: up to 8 units 15 mg strength presentation: Below 19 kg: up to 3 units 19 to 24 kg: up to 4 units 24 to 32 kg: up to 5 units 32 to 47 kg: up to 8 units 47 kg and beyond: up to 8 units, plus up to 3 units of the 10 mg strength presentation
Restriction Summary 13314 / ToC: 13292: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 2 pharmacological growth hormone stimulation tests (e.g. arginine, clonidine, glucagon, insulin); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 pharmacological growth hormone stimulation test (e.g. arginine, clonidine, glucagon, insulin) and 1 physiological growth hormone stimulation test (e.g. sleep, exercise); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) with other evidence of growth hormone deficiency, including septo-optic dysplasia (absent corpus callosum and/or septum pellucidum), midline abnormality including optic nerve hypoplasia, cleft lip and palate, midfacial hypoplasia and central incisor, ectopic and/or absent posterior pituitary bright spot, absent empty sella syndrome, hypoplastic anterior pituitary gland and/or pituitary stalk/infundibulum, and genetically proven biochemical growth hormone deficiency either isolated or as part of hypopituitarism in association with pituitary deficits (ACTH, TSH, GnRH or vasopressin/ADH deficiency); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels; or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGFBP-3 levels
	AND
	Clinical criteria:

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	Patient must have a current height at or below the 1st percentile for age and sex; or
	Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and a growth velocity below the 25th percentile for bone age and sex measured over a 12 month interval (or a 6 month interval for an older child); or
	Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and an annual growth velocity of 14 cm per year or less if the patient has a chronological age of 2 years or less; or
	Patient must have a current height above the 1st and at or below the 25th percentiles for age and sex and an annual growth velocity of 8 cm per year or less if the patient has a bone or chronological age of 2.5 years or less
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must not have previously received treatment under the PBS S100 Growth Hormone Program
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. (a) A minimum of 12 months of recent growth data (height and weight measurements) or a minimum of 6 months of recent growth data for an older child. The most recent data must not be more than three months old at the time of application; or (b) Height and weight measurements, not more than three months old at the time of application, for a patient whose current height is at or below the 1 st percentile for age and sex. 2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years. 3. Evidence of biochemical growth hormone deficiency, including the type of tests performed and peak growth hormone concentrations.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions:

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	Biochemical growth hormone deficiency should not be secondary to an intracranial lesion or cranial irradiation for applications under this category.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13319 / ToC: 13297: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Recommencement of treatment
	Treatment criteria:
	Patient must be undergoing recommencing treatment following a temporary treatment break (i.e. a lapse) from this drug for the stated indication above - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) reclassify the PBS indication
	Clinical criteria:
	Patient must have had a lapse in growth hormone treatment
	AND
	Clinical criteria:
	The treatment must not be for the purposes of resuming treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. Recent growth data (height and weight, not older than three months). 2. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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).

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	Prescribing Instructions: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
	Administrative Advice: If recommencement of treatment is sought under a different indication than that under which the patient was previously receiving treatment an application for <i>recommencement of treatment as a reclassified patient</i> should be submitted.
Restriction Summary 13305 / ToC: 13298: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Recommencement of treatment as a reclassified patient
	Treatment criteria:
	Patient must be undergoing treatment that is simultaneously: (a) recommencing treatment following a temporary break in treatment (i.e. a lapse), plus (b) reclassifying the PBS indication whilst continuing with the same growth hormone; subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) reclassify the PBS indication where the most recent authority approval was for a different growth hormone
	Clinical criteria:
	Patient must have had a lapse in growth hormone treatment
	AND
	Clinical criteria:
	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height at or below the 1st percentile for age and sex immediately prior to commencing treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and a growth velocity below the 25th percentile for bone age and sex measured over the 12 month interval immediately prior to commencement of treatment (or the 6 month interval immediately prior to commencement of treatment if the patient was an older child at commencement of treatment); or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 14 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a chronological age of 2 years or less at commencement of treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 8 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a bone or chronological age of 2.5 years or less at commencement of treatment
	AND
	Clinical criteria:
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 2 pharmacological growth hormone stimulation tests (e.g. arginine, clonidine, glucagon, insulin); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 pharmacological growth hormone stimulation test (e.g. arginine, clonidine, glucagon, insulin) and 1 physiological growth hormone stimulation test (e.g. sleep, exercise); or

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	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) with other evidence of growth hormone deficiency, including septo-optic dysplasia (absent corpus callosum and/or septum pellucidum), midline abnormality including optic nerve hypoplasia, cleft lip and palate, midfacial hypoplasia and central incisor, ectopic and/or absent posterior pituitary bright spot, absent empty sella syndrome, hypoplastic anterior pituitary gland and/or pituitary stalk/infundibulum, and genetically proven biochemical growth hormone deficiency either isolated or as part of hypopituitarism in association with pituitary deficits (ACTH, TSH, GnRH or vasopressin/ADH deficiency); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels; or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. (a) A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where a patient had a chronological age greater than 2.5 years at commencement of treatment); OR (b) Height and weight measurements from within three months prior to commencement of treatment for a patient whose height was at or below the 1 st percentile for age plus sex immediately prior to commencing treatment. 2. Evidence of biochemical growth hormone deficiency, including the type of tests performed and peak growth hormone concentrations. 3. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 4. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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:

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	Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: Biochemical growth hormone deficiency should not be secondary to an intracranial lesion or cranial irradiation for applications under this category.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13291 / ToC: 13284: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have a current height at or below the 1st percentile for age and sex
	AND
	Clinical criteria:
	Patient must have a growth velocity below the 25th percentile for bone age and sex measured over a 12 month interval (or a 6 month interval for an older child); or
	Patient must have an annual growth velocity of 8 cm per year or less if the patient has a bone or chronological age of 2.5 years or less
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must not have previously received treatment under the PBS S100 Growth Hormone Program
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7 cm; or
	Patient must be female and must not have a height greater than or equal to 155.0 cm
	AND
	Clinical criteria:
	Patient must be male and must not have maturational or constitutional delay in combination with an estimated mature height equal to or above 160.1 cm; or
	Patient must be female and must not have maturational or constitutional delay in combination with an estimated mature height equal to or above 148.0 cm
	Treatment criteria:
	Must be treated by a specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology
	AND
	Treatment criteria:

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	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. A minimum of 12 months of recent growth data (height and weight measurements) or a minimum of 6 months of recent growth data for an older child. The most recent data must not be more than three months old at the time of application. 2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years. 3. Confirmation of the patient's maturational or constitutional delay status. 4. If the patient has maturational or constitutional delay, confirmation that the patient has an estimated mature height below the 1 st adult height percentile.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13281 / ToC: 13304: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Recommencement of treatment
	Treatment criteria:
	Patient must be undergoing recommencing treatment following a temporary treatment break (i.e. a lapse) from this drug for the stated indication above - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) reclassify the PBS indication
	Clinical criteria:
	Patient must have had a lapse in growth hormone treatment
	AND
	Clinical criteria:
	The treatment must not be for the purposes of resuming treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity

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	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7cm; or
	Patient must be female and must not have a height greater than or equal to 155.0cm
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions:
	Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include:
	1. Recent growth data (height and weight, not older than three months).
	2. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions:
	If the application is submitted through HPOS form upload or mail, it must include:
	(i) A completed authority prescription form; and
	(ii) 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:
	Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions:
	Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions:
	In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
	Administrative Advice:
	If recommencement of treatment is sought under a different indication than that under which the patient was previously receiving treatment an application for <i>recommencement of treatment as a reclassified patient</i> should be submitted.
Restriction Summary 13283 / ToC: 13282: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Recommencement of treatment as a reclassified patient
	Treatment criteria:
	Patient must be undergoing treatment that is simultaneously: (a) recommencing treatment following a temporary break in treatment (i.e. a lapse), plus (b) reclassifying the PBS indication whilst continuing with the same growth hormone; subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) reclassify the PBS indication where the most recent authority approval was for a different growth hormone
	Clinical criteria:
	Patient must have had a lapse in growth hormone treatment
	AND

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	Clinical criteria:
	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height no higher than the 1st percentile for age plus sex at the time treatment first commenced
	AND
	Clinical criteria:
	Patient must have had a growth velocity below the 25th percentile for bone age plus sex measured over a 12 month interval (or a 6 month interval for an older child) prior to having commenced treatment; or
	Patient must have had an annual growth velocity of no higher than 8 cm per year where the patient had either a bone/chronological age no higher than 2.5 years prior to having commenced treatment
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7 cm; or
	Patient must be female and must not have a height greater than or equal to 155.0 cm
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions:
	An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions:
	Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include:
	1. A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where the patient had a chronological age greater than 2.5 years at commencement of treatment.
	2. Recent growth data (height and weight, not older than three months).
	3. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions:
	If the application is submitted through HPOS form upload or mail, it must include:
	(i) A completed authority prescription form; and
	(ii) 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).

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	Prescribing Instructions: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.

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Category / Program: Section 100 – Growth Hormone Program					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SOMAPACITAN					
somapacitan 5 mg/1.5 mL injection, 1.5 mL pen device	NEW 4 MP	7	7	1	Sogroya
somapacitan 10 mg/1.5 mL injection, 1.5 mL pen device	NEW 5 MP	6	6	1	Sogroya
somapacitan 15 mg/1.5 mL injection, 1.5 mL pen device	NEW 6 MP	6	6	1	Sogroya
Common Administrative Advice that applies to each restriction summary within this prescribing rule:					
	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. 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 authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can 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				
	Administrative Advice: An appropriate amount of drug (maximum quantity in units) for this treatment phase listing (approximately 13 weeks of treatment, which equates to at least 12 doses) per dispensing for various patient weight ranges, is outlined below: 5 mg strength presentation: Below 10 kg: up to 4 units 10 to 12 kg: up to 7 units 10 mg strength presentation: Below 10 kg: up to 2 units 10 to 16 kg: up to 3 units 16 to 21 kg: up to 4 units 21 to 25 kg: up to 6 units 15 mg strength presentation: Below 16 kg: up to 2 units 16 to 24 kg: up to 3 units 24 to 32 kg: up to 4 units 32 to 47 kg: up to 6 units 47 kg and beyond: up to 6 units, plus up to 2 units of the 10 mg strength presentation				
Restriction Summary 13286 / ToC: 13311: Authority Required					
	Indication: Short stature associated with biochemical growth hormone deficiency				
	Treatment Phase: Continuing treatment				

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	Treatment criteria:
	Patient must be undergoing continuing PBS-subsidised therapy with this drug - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) recommence treatment, (iv) reclassify the PBS indication
	Clinical criteria:
	Patient must have achieved the 50th percentile growth velocity for bone age plus sex following the most recent supply; or
	Patient must have achieved an increase in height standard deviation score for chronological age plus sex following the most recent supply; or
	Patient must have achieved a minimum growth velocity of 4 cm per year following the most recent supply; or
	Patient must have achieved a mid-parental height standard deviation score following the most recent supply; or
	The treatment must have been administered at a dose that is lower than that recommended in the approved Product Information in the most recent supply
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years. 3. The final adult height (in cm) of the patient's mother and father (where available).
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13300 / ToC: 13288: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Change of drug
	Treatment criteria:

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	Patient must be undergoing existing PBS-subsidised growth hormone treatment where the prescribed drug is changing within the same PBS indication - subsidy through this treatment phase must not: (i) initiate treatment, (ii) recommence treatment, (iii) reclassify the PBS indication
	Clinical criteria:
	Patient must have been treated with PBS-subsidised growth hormone for less than 32 weeks; or
	Patient must have been treated with PBS-subsidised growth hormone for at least 32 weeks, with an adequate response to treatment (as defined further below) having been demonstrated; or
	Patient must have been treated with PBS-subsidised growth hormone for at least 32 weeks, with an adequate response to treatment (as defined further below) not demonstrated due to at least one of: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance to treatment arising from social/family problems, (v) sub-optimal dosing (i.e. the dose was less than the permitted upper dose range)
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: Definition: An adequate response to the preceding supply of growth hormone for which the patient is changing from is one where the patient, for their sex, has achieved at least one of: (a) the 50 th percentile growth velocity for bone age; (b) an increase in height standard deviation score for chronological age; (c) a minimum growth velocity of 4 cm per year; (d) a mid-parental height standard deviation score.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years. Where growth data has been supplied within 3 months of this authority application, do not resupply this data.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.

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	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13287 / ToC: 13287: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Continuing treatment as a reclassified patient
	Treatment criteria:
	Patient must be undergoing continuing PBS-subsidised therapy with this drug where the most recent authority approval for this drug was for a different PBS indication to that stated above - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) recommence treatment, (iv) reclassify the PBS indication where the most recent authority approval was for a different growth hormone, (v) reclassify the PBS indication and recommence treatment simultaneously
	Clinical criteria:
	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height at or below the 1st percentile for age and sex immediately prior to commencing treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and a growth velocity below the 25th percentile for bone age and sex measured over the 12 month interval immediately prior to commencement of treatment (or the 6 month interval immediately prior to commencement of treatment if the patient was an older child at commencement of treatment); or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 14 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a chronological age of 2 years or less at commencement of treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 8 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a bone or chronological age of 2.5 years or less at commencement of treatment
	AND
	Clinical criteria:
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 2 pharmacological growth hormone stimulation tests (e.g. arginine, clonidine, glucagon, insulin); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 pharmacological growth hormone stimulation test (e.g. arginine, clonidine, glucagon, insulin) and 1 physiological growth hormone stimulation test (e.g. sleep, exercise); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) with other evidence of growth hormone deficiency, including septo-optic dysplasia (absent corpus callosum and/or septum pellucidum), midline abnormality including optic nerve hypoplasia, cleft lip and palate, midfacial hypoplasia and central incisor, ectopic and/or absent posterior pituitary bright spot, absent empty sella syndrome, hypoplastic anterior pituitary gland and/or pituitary stalk/infundibulum, and genetically proven biochemical growth hormone deficiency either isolated or as part of hypopituitarism in association with pituitary deficits (ACTH, TSH, GnRH or vasopressin/ADH deficiency); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels; or

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	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGFBP-3 levels
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. (a) A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where a patient had a chronological age greater than 2.5 years at commencement of treatment); OR (b) Height and weight measurements from within three months prior to commencement of treatment for a patient whose height was at or below the 1 st percentile for age plus sex immediately prior to commencing treatment. 2. Evidence of biochemical growth hormone deficiency, including the type of tests performed and peak growth hormone concentrations. 3. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 4. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: Biochemical growth hormone deficiency should not be secondary to an intracranial lesion or cranial irradiation for applications under this category.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.

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Restriction Summary 13301 / ToC: 13294: Authority Required	
	Indication: Short stature associated with biochemical growth hormone deficiency
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Treatment criteria:
	Patient must be undergoing privately funded treatment (e.g. through a clinical trial, a sponsor compassionate access program, supply from an overseas jurisdiction) with this drug at the time of this authority application - subsidy through this treatment phase must only occur once per lifetime
	Clinical criteria:
	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height at or below the 1st percentile for age and sex immediately prior to commencing treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and a growth velocity below the 25th percentile for bone age and sex measured over the 12 month interval immediately prior to commencement of treatment (or the 6 month interval immediately prior to commencement of treatment if the patient was an older child at commencement of treatment); or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 14 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a chronological age of 2 years or less at commencement of treatment; or
	Patient must have had both a height above the 1st and at or below the 25th percentiles for age and sex immediately prior to commencing treatment and an annual growth velocity of 8 cm per year or less in the 12 month period immediately prior to commencement of treatment, if the patient had a bone or chronological age of 2.5 years or less at commencement of treatment
	AND
	Clinical criteria:
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 2 pharmacological growth hormone stimulation tests (e.g. arginine, clonidine, glucagon, insulin); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 pharmacological growth hormone stimulation test (e.g. arginine, clonidine, glucagon, insulin) and 1 physiological growth hormone stimulation test (e.g. sleep, exercise); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) with other evidence of growth hormone deficiency, including septo-optic dysplasia (absent corpus callosum and/or septum pellucidum), midline abnormality including optic nerve hypoplasia, cleft lip and palate, midfacial hypoplasia and central incisor, ectopic and/or absent posterior pituitary bright spot, absent empty sella syndrome, hypoplastic anterior pituitary gland and/or pituitary stalk/infundibulum, and genetically proven biochemical growth hormone deficiency either isolated or as part of hypopituitarism in association with pituitary deficits (ACTH, TSH, GnRH or vasopressin/ADH deficiency); or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGF-1 levels; or
	Patient must have evidence of biochemical growth hormone deficiency, with a peak serum growth hormone concentration less than 10 mU/L or less than or equal to 3.3 micrograms per litre in response to 1 growth hormone stimulation test (pharmacological or physiological e.g. arginine, clonidine, glucagon, insulin, sleep, exercise) and low plasma IGFBP-3 levels
	AND
	Clinical criteria:

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	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. (a) A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where a patient had a chronological age greater than 2.5 years at commencement of treatment); OR (b) Height and weight measurements from within three months prior to commencement of treatment for a patient whose height was at or below the 1 st percentile for age plus sex immediately prior to commencing treatment. 2. Evidence of biochemical growth hormone deficiency, including the type of tests performed and peak growth hormone concentrations. 3. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 4. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: Biochemical growth hormone deficiency should not be secondary to an intracranial lesion or cranial irradiation for applications under this category.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13302 / ToC: 13308: Authority Required	
	Indication: Short stature and slow growth

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	Treatment Phase: Continuing treatment
	Treatment criteria:
	Patient must be undergoing continuing PBS-subsidised therapy with this drug - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) recommence treatment, (iv) reclassify the PBS indication
	Clinical criteria:
	Patient must have previously received treatment under the PBS S100 Growth Hormone Program under the short stature and slow growth category
	AND
	Clinical criteria:
	Patient must have achieved the 50th percentile growth velocity for bone age plus sex following the most recent supply; or
	Patient must have achieved an increase in height standard deviation score for chronological age plus sex following the most recent supply; or
	Patient must have achieved a minimum growth velocity of 4 cm per year following the most recent supply; or
	Patient must have achieved a mid-parental height standard deviation score following the most recent supply; or
	The treatment must have been administered at a dose that is lower than that recommended in the approved Product Information in the most recent supply
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7cm; or
	Patient must be female and must not have a height greater than or equal to 155.0cm
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions:
	Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include:
	1. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months.
	2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years.
	3. The final adult height (in cm) of the patient's mother and father (where available).
	Prescribing Instructions:
	If the application is submitted through HPOS form upload or mail, it must include:
	(i) A completed authority prescription form; and
	(ii) 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:
	Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions:
	Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions:

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	In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13315 / ToC: 13309: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Change of drug
	Treatment criteria:
	Patient must be undergoing existing PBS-subsidised growth hormone treatment where the prescribed drug is changing within the same PBS indication - subsidy through this treatment phase must not: (i) initiate treatment, (ii) recommence treatment, (iii) reclassify the PBS indication
	Clinical criteria:
	Patient must have been treated with PBS-subsidised growth hormone for less than 32 weeks; or
	Patient must have been treated with PBS-subsidised growth hormone for at least 32 weeks, with an adequate response to treatment (as defined further below) having been demonstrated; or
	Patient must have been treated with PBS-subsidised growth hormone for at least 32 weeks, with an adequate response to treatment (as defined further below) not demonstrated due to at least one of: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance to treatment arising from social/family problems, (v) sub-optimal dosing (i.e. the dose was less than the permitted upper dose range)
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7cm; or
	Patient must be female and must not have a height greater than or equal to 155.0cm
	Treatment criteria:
	Must be treated by a specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a specialist or consultant physician in general paediatrics in consultation with a nominated specialist or consultant physician in paediatric endocrinology
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions:
	Definition: An adequate response to the preceding supply of growth hormone for which the patient is changing from is one where the patient, for their sex, has achieved at least one of: (a) the 50 th percentile growth velocity for bone age; (b) an increase in height standard deviation score for chronological age; (c) a minimum growth velocity of 4 cm per year; (d) a mid-parental height standard deviation score.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include:

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	1. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 2. A bone age result performed within the last 12 months where the patient has a chronological age greater than 2.5 years. Where growth data has been supplied within 3 months of this authority application, do not resupply this data.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13299 / ToC: 13312: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Continuing treatment as a reclassified patient
	Treatment criteria:
	Patient must be undergoing continuing PBS-subsidised therapy with this drug where the most recent authority approval for this drug was for a different PBS indication to that stated above - subsidy through this treatment phase must not: (i) initiate treatment, (ii) change the prescribed drug, (iii) recommence treatment, (iv) reclassify the PBS indication where the most recent authority approval was for a different growth hormone, (v) reclassify the PBS indication and recommence treatment simultaneously
	Clinical criteria:
	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height no higher than the 1st percentile for age plus sex at the time treatment first commenced
	AND
	Clinical criteria:
	Patient must have had a growth velocity below the 25th percentile for bone age plus sex measured over a 12 month interval (or a 6 month interval for an older child) prior to having commenced treatment; or
	Patient must have had an annual growth velocity of no higher than 8 cm per year where the patient had either a bone/chronological age no higher than 2.5 years prior to having commenced treatment
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or

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	Patient must be female and must not have a bone age of 13.5 years or more
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7cm; or
	Patient must be female and must not have a height greater than or equal to 155.0cm
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: An older child is defined as a male with a chronological age of at least 12 years or a bone age of at least 10 years, or a female with a chronological age of at least 10 years or a bone age of at least 8 years.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where the patient had a chronological age greater than 2.5 years at commencement of treatment. 2. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 3. A bone age result performed within the last 12 months where a patient has a chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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: Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.
Restriction Summary 13310 / ToC: 13318: Authority Required	
	Indication: Short stature and slow growth
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Treatment criteria:
	Patient must be undergoing privately funded treatment (e.g. through a clinical trial, a sponsor compassionate access program, supply from an overseas jurisdiction) with this drug at the time of this authority application - subsidy through this treatment phase must only occur once per lifetime
	Clinical criteria:

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	The treatment must not be for the purposes of continuing treatment that is known to be non-efficacious for the patient - where an inadequate response has been observed for the most recent supply of this drug, it must have been confounded by at least one of the following: (i) a significant medical illness, (ii) major surgery (e.g. renal transplant), (iii) an adverse reaction to growth hormone, (iv) non-compliance due to social/family problems, (v) a lower than recommended (as specified by this drug's approved Product Information) dose
	AND
	Clinical criteria:
	Patient must have had a height no higher than the 1st percentile for age plus sex at the time treatment first commenced
	AND
	Clinical criteria:
	Patient must have had a growth velocity below the 25th percentile for bone age plus sex measured over a 12 month interval (or a 6 month interval for an older child) prior to having commenced treatment; or
	Patient must have had an annual growth velocity of no higher than 8 cm per year where the patient had either a bone/chronological age no higher than 2.5 years prior to having commenced treatment
	AND
	Clinical criteria:
	Patient must not have a condition with a known risk of malignancy including chromosomal abnormalities such as Down and Bloom syndromes
	AND
	Clinical criteria:
	Patient must not have an active tumour or evidence of tumour growth or activity
	AND
	Clinical criteria:
	Patient must be male and must not have a height greater than or equal to 167.7 cm; or
	Patient must be female and must not have a height greater than or equal to 155.0 cm
	AND
	Clinical criteria:
	Patient must be male and must not have a bone age of 15.5 years or more; or
	Patient must be female and must not have a bone age of 13.5 years or more
	Treatment criteria:
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in paediatric endocrinology; or
	Must be treated by a medical practitioner in consultation with a nominated specialist or consultant physician in general paediatrics
	AND
	Treatment criteria:
	Patient must be undergoing treatment for the stated indication with only one growth hormone at any given time
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: 1. (a) A minimum of 12 months of growth data (height and weight measurements) from immediately prior to commencement of treatment, or a minimum of 6 months of growth data from immediately prior to commencement of treatment if the patient was an older child at commencement of treatment; and the result of a bone age assessment performed within the 12 months immediately prior to commencement of treatment where a patient had a chronological age greater than 2.5 years at commencement of treatment; OR (b) Height and weight measurements from within three months prior to commencement of treatment for a patient whose height was at or below the 1 st percentile for age plus sex immediately prior to commencing treatment. 2. Growth data (height and weight) for the most recent 6 month treatment period, including data at both the start and end of the treatment period. The most recent data must not be older than three months. 3. A bone age result performed within the last 12 months where the patient has chronological age greater than 2.5 years.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) A completed authority prescription form; and (ii) 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:

	Prescribe an appropriate amount of drug (maximum quantity in units) outlined within the 'Notes' section of this restriction.
	Prescribing Instructions: Prescribers must keep a copy of any clinical records relating to the prescription, including such records required to demonstrate that the prescription was written in compliance with any relevant circumstances and/or purposes. These records must be kept for 2 years after the date the prescription to which the records relate is written.
	Prescribing Instructions: In children with diabetes mellitus prescribers must ascertain that a growth failure is not due to poor diabetes control, diabetes control is adequate, and regular screening occurs for diabetes complications, particularly retinopathy.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.