

DORSET MEDICINES ADVISORY GROUP

COMMISSIONING STATEMENT ON THE USE OF GROWTH HORMONE FOR CHILDREN AND ADULTS.

The use of growth hormone (somatropin) will be commissioned by NHS Dorset Clinical Commissioning Group in line with NICE TA 188 and TA 64. The commissioners expect one of the most cost effective products on the market to be the first line option for treatment:

- Genotropin®
- Humatrope®
- Omnitrope®

Where this is not deemed to be clinically appropriate, after assessment of and discussion with the patient and / or their carer and taking into consideration therapeutic need and the likelihood of adherence to treatment, and a more costly product is recommended the commissioners expect this to be applied for via the prior approval application process. For patients already established on therapy clinicians are strongly encouraged to recommend a switch from a less cost effective appointment to a more cost effective product at the next available appointment.

MARKETING AUTHORISATION AND MODE OF ACTION

- 1.1 Growth hormone is used to treat deficiency of the hormone in children and adults. In children, it is used in Prader-Willi syndrome, Turner syndrome, and chronic renal insufficiency, short children considered small for gestational age at birth and short stature homeobox-containing gene (SHOX) deficiency.
- 1.2 There are several brands of somatropin available which are listed with licence and costs at Appendix A.
- 1.3 Human growth hormone is produced by the anterior pituitary gland and is essential for normal growth in children. Growth failure (short stature) is defined as a height that lies below two standard deviations from the mean for a patient's age and gender. Growth hormone deficiency (GH) deficiency affects about one in 3,500 children.
- 1.4 Somatropin works by stimulating the hormone, insulin-like growth factor 1 (IGF-1) leading to increased bone growth, muscle strength, cardiac output and production of IGF binding proteins (IGFBP). Of the seven preparations of somatropin listed above all but Omnitrope® are innovator products. Omnitrope® is a bio similar product of Genotropin®. Genotropin® and Omnitrope® possess the broadest range of licensed indications.

2. NICE APPRAISAL

TA 188: Human growth hormone (somatropin) for the treatment of growth failure in children

2.1 Somatropin (recombinant human growth hormone) is recommended as a treatment option for children with growth failure associated with any of the following conditions:

- Growth hormone deficiency
- Turner syndrome
- Prader–Willi syndrome
- Chronic renal insufficiency
- Born small for gestational age with subsequent growth failure at 4 years of age or later
- Short stature homeobox-containing gene (*SHOX*) deficiency.

2.2 Treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth hormone disorders in children. The choice of product should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of the products available, taking into consideration therapeutic need and the likelihood of adherence to treatment. If, after that discussion, more than one product is suitable, the least costly product should be chosen.

2.3 Treatment with somatropin should be discontinued if any of the following apply:

- Growth velocity increases less than 50% from baseline in the first year of treatment,
- Final height is approached and growth velocity is less than 2cm total growth in 1 year
- There are insurmountable problems with adherence
- Final height is attained.

In Prader-Willi syndrome evaluation of response to therapy should also consider body composition.

Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or carers either by

- A paediatrician with specialist expertise in managing growth hormone disorders in children, or
- An adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

TA 64: Human growth hormone (somatropin) in adults with growth hormone deficiency

- 2.4 Recombinant human growth hormone (somatropin) treatment is recommended for the treatment of adults with growth hormone (GH) deficiency only if they fulfill all three of the following criteria.
- They have severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test.
 - They have a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire.
 - They are already receiving treatment for any other pituitary hormone deficiencies as required.
- 2.5 The QoL status of people who are given GH treatment should be re-assessed 9 months after the initiation of therapy (an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period). GH treatment should be discontinued for those people who demonstrate a QoL improvement of less than 7 points in QoL-AGHDA score.
- 2.6 Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved, provided they satisfy the biochemical criteria for severe GH deficiency (defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test). After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on all the criteria in 2.4
- 2.7 Patients currently receiving GH treatment, for the management of adult onset GH deficiency, whether as routine therapy or as part of a clinical trial, could suffer loss of well being if their treatment were to be discontinued at a time they did not anticipate. Because of this, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop.
- 2.8 Children with GH deficiency should be treated as outlined in the Institute's guidance on the use of GH in children (*NICE Technology Appraisal Guidance No. 42*). At completion of linear growth (that is, growth rate < 2 cm/year), GH treatment should be stopped for 2–3 months, and then GH status should be re-assessed. GH treatment at adult doses should be re-started only in those satisfying the biochemical criteria for severe GH deficiency (defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test), and continued until adult peak bone mass has been achieved (normally around 25 years of age). After adult peak bone mass has been

achieved, the decision to continue GH treatment should be based on all the criteria set out in 2.4.

- 2.9 Initiation of GH treatment, dose titration and assessment of response during trial periods should be undertaken by a consultant endocrinologist with a special interest in the management of GH disorders. Thereafter, if maintenance treatment is to be prescribed in primary care, it is recommended that this should be under an agreed shared-care protocol.

3. ASSESSMENT OF THE COST IMPLICATIONS

- 3.1 TA 64 states within its comments on implications for the NHS: Although it is hard to estimate the number of eligible patients accurately, it is anticipated that only a small proportion of adults with GH deficiency will achieve sustained improvement of at least 7 points on the QoL-AGHDA scale at the end of the assessment period (that is, 9 months). If it is assumed that 30% of adult-onset and 10% of childhood-onset patients will fulfil the starting criteria, and of these 40% will fail to achieve an improvement of at least 7 points on the QoL-AGHDA scale, there will be around 1180 people in England and Wales who would be eligible for continuous GH treatment. This is less than the estimated number of patients currently receiving GH treatment, so implementing this guidance will not incur any additional costs to the NHS. However, in the absence of more accurate data on future uptake, it is not possible to indicate the scale of any potential savings.
- 3.2 Appendix A demonstrates that there is a wide range of products at varying costs/mg. Where more than one product is suitable for a patient the most cost-effective licensed option should be offered. The most cost-effective options are currently Genotropin[®], Humatrope[®], and Omnitrope[®]. Their relevant licensed indications are provided in Appendix A.

References

1. Human growth hormone (Somatropin) for the treatment of growth failure in children <https://www.nice.org.uk/guidance/ta188>
2. Human growth hormone (Somatropin) in adults with growth hormone deficiency <https://www.nice.org.uk/guidance/ta64>
3. Electronic Medicines Compendium: <http://www.medicines.org.uk/emc/search>

Approved by	Dorset Medicines Advisory Group		
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Produced by (Title);	Michelle Trevett, Senior Pharmacist, NHS Dorset CCG		
Reviewed	October 2016		
Review Date:	October 2018 or before in light of new information of either SHA guidance or NICE publications.		

Appendix A

Brand	Licensed indications	Cost (correct at October 2016)
<p>Genotropin® (Pharmacia)</p>	<p><u>Children</u></p> <p>Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD) and growth disturbance associated with Turner syndrome or chronic renal insufficiency.</p> <p>Growth disturbance [current height standard deviation score (SDS) < - 2.5 and parental adjusted height SDS < - 1] in short children born small for gestational age (SGA), with a birth weight and/or length below - 2 SD, who failed to show catch-up growth [height velocity (HV) SDS < 0 during the last year] by 4 years of age or later.</p> <p>Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.</p> <p><u>Adults</u></p> <p>Replacement therapy in adults with pronounced growth hormone deficiency.</p> <p><i>Adult Onset:</i> Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency.</p> <p><i>Childhood Onset:</i> Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a pituitary/hypothalamic disease or insult, an insulin-like growth factor-I (IGF-I) SDS < - 2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD.</p> <p>All other patients will require IGF-I assay and one</p>	<p>£17.39/mg</p> <p>As Somatropin (RBE)</p> <p><u>As Genotropin MiniQuick:</u></p> <p>0.2mg x 7 - £24.35</p> <p>0.4mg x 7 - £48.69</p> <p>0.6mg x 7 - £73.04</p> <p>0.8mg x 7 - £97.38</p> <p>1mg x 7 - £121.73</p> <p>1.2mg x7 - £146.08</p> <p>1.4mg x 7 - £170.42</p> <p>1.6mg x7 - £194.77</p> <p>1.8mg x7 - £219.11</p> <p>2mg x 7 - £243.46</p> <p><u>As Genotropin Go Quick</u></p> <p>5.3mg pre-filled pen - £92.15</p> <p>12mg pre-filled pen - £208.65</p>

	growth hormone stimulation test.	
Humatrope® (Lilly)	<p><i>Paediatric Patients</i></p> <p>HUMATROPE is indicated for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.</p> <p>HUMATROPE is also indicated for the treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis.</p> <p>HUMATROPE is also indicated for the treatment of growth retardation in prepubertal children with chronic renal insufficiency.</p> <p>HUMATROPE is also indicated for the treatment of patients who have growth failure associated with SHOX deficiency, as confirmed by DNA analysis.</p> <p>HUMATROPE is also indicated for growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (height velocity SDS < 0 during the last year) by 4 years of age or later.</p> <p><i>Adult Patients</i></p> <p>HUMATROPE is indicated for replacement therapy in adults with pronounced growth hormone deficiency.</p> <p>Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations <-2 SDS, who may be considered for one test. The cut-off point of the dynamic test should be strict.</p>	<p>£18/mg</p> <p>As somatropin (RBE)</p> <p>6mg prefilled syringe - £108.00</p> <p>12mg prefilled syringe - £216.00</p> <p>24mg prefilled syringe - £432.00</p>

<p>Norditropin® (Novo Nordisk)</p>	<p><u>Children:</u></p> <p>Growth failure due to growth hormone deficiency (GHD)</p> <p>Growth failure in girls due to gonadal dysgenesis (Turner syndrome)</p> <p>Growth retardation in prepubertal children due to chronic renal disease</p> <p>Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later.</p> <p><u>Adults:</u></p> <p><u>Childhood onset growth hormone deficiency:</u></p> <p>Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurements of IGF-I is < -2 SDS after at least four weeks off growth hormone treatment.</p> <p>In all other patients an IGF-I measurement and one growth hormone stimulation test is required.</p> <p><u>Adult onset growth hormone deficiency:</u></p> <p>Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.</p> <p>In adults, the insulin tolerance test is the provocative test of choice. When the insulin tolerance test is contraindicated, alternative provocative tests must be used. The combined arginine-growth hormone releasing hormone is recommended. An arginine or glucagon test may also be considered; however these tests have less established diagnostic value than the insulin tolerance test.</p>	<p>£31.91/mg</p> <p>As Somatropin (EPR)</p> <p><u>Norditropin® Simple XX</u></p> <p><u>NordiPen</u> 5mg/1.5ml - £106.35</p> <p><u>NordiPen</u> 10mg/1.5ml - £212.70</p> <p><u>NordiPen</u> 15mg/1.5ml - £319.05</p> <p><u>Norditropin NordiFlex</u> 5mg/1.5ml - £115.90</p> <p><u>Norditropin NordiFlex</u> 10mg/1.5ml - £231.80</p> <p><u>Norditropin NordiFlex</u> 15mg/1.5ml - £347.70</p>
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<p>NutropinAq® (Ipsen)</p>	<p>Long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion.</p> <p>- Long-term treatment of growth failure associated with Turner syndrome.</p> <p>- Treatment of prepubertal children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation.</p> <p>- Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset aetiology. Growth hormone deficiency should be confirmed appropriately prior to treatment (see section 4.4).</p>	<p>£40.60/mg</p> <p><u>As Nutropin AQ NuSpin</u></p> <p>Pen injection device 5mg/2ml £</p> <p>Pen injection device 10mg/2ml - £203.00</p> <p>Pen injection device 20mg/2ml £</p>
<p>Omnitrope® (Sandoz)</p>	<p><u>Infants, children and adolescents</u></p> <p>- Growth disturbance due to insufficient secretion of growth hormone (GH).</p> <p>- Growth disturbance associated with Turner syndrome.</p> <p>- Growth disturbance associated with chronic renal insufficiency.</p> <p>- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted SDS < -1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later.</p> <p>- Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.</p> <p><u>Adults</u></p> <p>- Replacement therapy in adults with pronounced growth hormone deficiency. Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations (SDS < -2) who may be considered for</p>	<p>£17.35/mg</p> <p>As Somatropin (RBE)</p> <p><u>Omnitrope Pen 5,</u> 5mg/1.5ml - £368.74</p> <p><u>Omnitrope pen 10,</u> 10mg/1.5ml - £737.49</p> <p><u>SurePal 5,</u> 5mg/1.5ml - £368.74</p> <p><u>SurePal 10,</u> 10mg/1.5ml - £737.49</p> <p><u>SurePal 15,</u> 15mg/1.5ml - £1106.22</p>

	one test. The cut-off point of the dynamic test should be strict.	
Saizen® EasyPod (Merck Serono)	<p>Saizen is indicated in the treatment of:</p> <p>Children and adolescents:</p> <ul style="list-style-type: none"> - Growth failure in children caused by decreased or absent secretion of endogenous growth hormone. - Growth failure in girls with gonadal dysgenesis (Turner Syndrome), confirmed by chromosomal analysis. - Growth failure in prepubertal children due to chronic renal failure (CRF). - Growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA) with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later. <p>Adults:</p> <ul style="list-style-type: none"> - Replacement therapy in adults with pronounced growth hormone deficiency as diagnosed by a single dynamic test for growth hormone deficiency. Patients must also fulfil the following criteria: <ul style="list-style-type: none"> - Childhood Onset: <p>Patients who were diagnosed as growth hormone deficient during childhood must be retested and their growth hormone deficiency confirmed before replacement therapy with Saizen is started.</p> - Adult Onset: <p>Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin</p> 	<p>£23.18/mg</p> <p>As Somatropin</p> <p><u>ClickEasy</u> 8mg powder - £185.44</p> <p><u>Easypod device</u> 5.83mg/ml, 1x1.03ml - £139.08</p> <p><u>Easypod device</u> 8mg/ml, 1x1.5ml - £278.16</p> <p><u>Easypod device</u> 8mg/ml, 1x2.5ml - £463.60</p>

<p>Zomacton® (Ferring)</p>	<p>Zomacton is indicated for:</p> <ul style="list-style-type: none"> - the long – term treatment of children who have growth failure due to inadequate secretion of growth hormone - The long-term treatment of growth retardation due to Turner's Syndrome confirmed by chromosome analysis. 	<p>£19.20/mg</p> <p>As Somatropin (RBE)</p> <p><u>ZomaJet 2</u> or <u>Auto-Jector</u> <u>devices</u> 4mg vial - £76.79</p> <p>10mg vial - £199.23</p>
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