NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA188; Human growth hormone for the treatment of growth failure in children (review of TA42)

This guidance was issued in May 2010.

The review date for this guidance is May 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To advise on the clinical and cost effectiveness of the use of human growth hormone in treatment of growth deficiencies and other growth failure in children.

3. Current guidance

1.1 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.

1.2 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.

1.3 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 2 cm 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.

4. Rationale[1]

There is no new evidence that has the potential to lead to a change in the recommendations. Also, the marketing authorisations for the interventions have not changed, no new interventions have come to market since technology appraisal 188 was issued, and there have been no marked changes in the prices of the interventions.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from June 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

7. Summary of evidence and implications for review

The marketing authorisations for the interventions in the original appraisal have not changed and no new interventions have come to market since technology appraisal 188 was issued. There have been no marked changes in the prices of the interventions.

Over 80 studies have reported since technology appraisal 188 was published. Almost all of them were small studies or focused on aspects of treatment that are not relevant to the scope of the appraisal, such as comparing dosages and different injection devices, which would not impact on the current recommendations.

However, some safety concerns have arisen. The French population-based cohort study, 'Santé Adulte GH Enfant' (SAGhE) is evaluating the long-term mortality of patients treated with recombinant GH in childhood in France using a population-based register. Investigators identified more than 10,000 young adults who started a recombinant growth hormone treatment between 1985 and 1996. From a preliminary analysis of approximately 7000 of these patients, the authors concluded that mortality rates were increased in this population of adults who had received recombinant GH as children, particularly in those who had received the highest doses. Specifically, increased death rates from bone tumours or cerebral haemorrhage were detected but not for all cancers (Carel et al. 2012).

These preliminary results triggered a review by the European Medicines Agency. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the study had significant methodological limitations and that the other safety data examined did not corroborate a potentially higher risk of mortality associated with somatropin-containing medicines. The CHMP therefore confirmed that the benefit–risk balance of these medicines remained positive, but took the opportunity of this review to harmonise the existing contraindications, warnings and precautions for these medicines throughout the European Union. The harmonised wording emphasises that somatropin must not be used if there is any evidence of a tumour activity, and that the recommended maximum daily dose should not be exceeded.

A new European safety and effectiveness study in about 30,000 patients is being conducted in 8 European countries (Belgium, France, Germany, Italy, the Netherlands, Sweden, Switzerland and the United Kingdom). Preliminary data from 2500 patients did not confirm those of the French SAGhE study(Savendahl et al. 2012).

In summary, the evidence suggests that it would not be necessary to review TA188 at present.

8. Implementation

A submission from Implementation is included in Appendix 3. Because the submission includes combined data from adults and children, it is not possible to draw any conclusions about the use of somatropin in children, which is the population appraised in TA188.

9. Equality issues

No equality issues were raised during the scoping process, in the evidence submissions or Committee discussions in the original appraisal.

GE paper sign off: Elisabeth George, 17 04 13

Contributors to this paper:

Information Specialist: Paul Levay

Technical Lead: Linda Landells

Implementation Analyst: Rebecca Lea

Project Manager: Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Human growth hormone (somatropin) in adults with growth hormone deficiency. TA64. Published: August 2003. Review: deferred for trial results (May 2012).

In progress

None

Referred - QSs and CGs

None

Suspended/terminated

None

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
3.1 In the UK, seven preparations of somatropin are available: Genotropin, Pfizer; Humatrope, Lilly; Norditropin, Novo Nordisk; NutropinAq, Ipsen; Omnitrope, Sandoz; Saizen, Merck Serono; Zomacton, Ferring. Each product is produced by recombinant DNA technology and has a sequence identical to that of human growth hormone produced by the pituitary gland. The licensed indications are as follows (for the different products the wording may differ): • growth disturbance in children due to insufficient secretion of growth hormone (growth hormone deficiency). • growth failure in girls associated with gonadal dysgenesis (Turner syndrome). • growth retardation in prepubertal children associated with chronic renal insufficiency (CRI). • improvement of growth and body composition in children with Prader–Willi syndrome. The diagnosis of Prader–Willi syndrome should be confirmed by appropriate genetic testing. • growth disturbance (current height standard deviation score [SDS] −2.5 and parental	No change. See the Summaries of Product Characteristics for the exact wording of the therapeutic indications. [redacted]

adjusted height SDS −1) in short children born small for gestational age, with a birth weight and/or length below −2 SD, who failed to show catch-up growth (height velocity SDS less than 0 during the past year) by 4 years of age or later. • growth failure associated with SHOX deficiency, as confirmed by DNA analysis. 3.2 The seven manufacturers have UK marketing authorisations for somatropin for the following indications: • Lilly (Humatrope): growth hormone deficiency; Turner syndrome; CRI; short children born small for gestational age and SHOX deficiency. • Ferring (Zomacton): growth hormone deficiency and Turner syndrome. • Ipsen (NutropinAq): growth hormone deficiency; Turner syndrome and CRI. • Novo Nordisk (Norditropin SimpleXx): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age. • Pfizer (Genotropin): growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age. • Sandoz (Omnitrope) [biosimilar]: growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age. • Merck Serono (Saizen): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age.	

Costs considered in original appraisal	Current costs
Genotropin (Pfizer): £23.18 per mg Humatrope (Lilly): £18.00 per mg Norditropin (Novo Nordisk): £21.39 per mg (since January 2010 £21.27 per mg), NutropinAq (Ipsen): £20.70 per mg Omnitrope (Sandoz): £18.26 per mg Saizen (Merck Serono): £23.18 per mg Zomacton (Ferring): £19.92 per mg Excluding VAT; British national formulary (BNF) edition 58 Costs may vary in different settings because of negotiated procurement discounts The cost of treatment with somatropin depends on the dose, which is determined by the weight or body surface area of the child as well as by the indication for growth hormone treatment.	Genotropin (Pfizer): 5.3-mg (16-unit) cartridge = £122.87 12-mg (36-unit) cartridge = £278.20 Humatrope (Lilly): 6-mg (18-unit) cartridge = £108.00 12-mg (36-unit) cartridge = £216.00 24-mg (72-unit) cartridge = £432.00 Norditropin (Novo Nordisk): 3.3 mg (10 units)/mL, net price 5-mL (5-mg, 15-unit) cartridge = £106.35; 6.7 mg (20 units)/mL, 1.5-mL (10-mg, 30-unit) cartridge = £212.70 10 mg (30 units)/mL, 1.5-mL (15-mg, 45-unit) cartridge = £319.05 NutropinAq (Ipsen): 10 mg (30 units) 2-ml cartridge = £203.00 Omnitrope (Sandoz): 3.3 mg (10 units)/mL, net price 1.5 mL (5-mg, 15-unit) cartridge = £86.77 6.7 mg (20 units)/mL, 1.5 mL (10-mg, 30-unit) cartridge = £173.50 Saizen (Merck Serono): 5.83 mg (17.5 units)/mL, net price 1.03-mL (6-mg, 18-unit) cartridge = £139.08 8 mg (24 units)/mL, 1.5-mL (12-mg, 36-unit) cartridge = £278.16 2.5-mL (20-mg, 60-unit) cartridge = £463.60 Zomacton (Ferring): 4-mg (12-unit) vial (with diluent) = £79.69 All prices excluding VAT. BNF, March 2013

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date)
hGH-CTP (PROLOR Biotech)	Longer-Acting Human Growth Hormone, to be administered once weekly. Granted EU orphan drug designation Feb 2013. In Phase 2 clinical trials for children and proceeding to Phase 3 in adults in 2013.

Registered and unpublished trials

Trial name and registration number	Details
Safety and Appropriateness of Growth Hormone treatments in Europe UKCRN 10191	Observational cohort study Enrolment: 30,000 Closure: June 2013 [cited in TA188 research recommendations]
Neuromuscular Changes In Small For Gestational Age Children During Somatropin Therapy (SGA-POWER) NCT00625872	Status: terminated due to low recruitment (not safety reasons) Results available [cited in TA188 research recommendations]
Somatropin Treatment in Patients With SHOX Deficiency and Turner Syndrome NCT00190658	Status: completed December 2010 Enrolment: 75 [cited in TA188 research recommendations]
Long-Term Growth and Skeletal Effects of Early Growth Hormone Treatment in Turner Syndrome Phase IV NCT00266656	Status: recruiting Purpose: to determine whether girls who received 2 years of GH treatment before 6 years of age achieve taller adult height than girls who were untreated during this time. Methods: Open Label Parallel Assignment Enrolment: 88 Completion: October 2015
A Randomized, Open-label, Two-arm Parallel Group, No Treatment Group-controlled, Multicenter Phase III Study to Evaluate the Safety and Efficacy of Saizen 0.067 mg/kg/Day Subcutaneous Injection in Children With Idiopathic Short Stature NCT01746862	Status: recruiting Enrolment: 87 Completion: November 2015

Trial name and registration number	Details
A Two-Year Multi-Centre, Randomized Two Arm Study Of Genotropin Treatment In Very Young Children Born Small For Gestational Age: Early Growth And Neurodevelopment NCT00627523	Status: recruiting Enrolment: 42 Completion: December 2013
Long-term Safety Follow-up After Growth Hormone Treatment (rhGH) of Short Children Born Small for Gestational Age (SGA), Sandoz NCT01491854	Status: recruiting Purpose: to evaluate the long-term effect of development of diabetes for 10 years after the end of treatment. Enrolment: 200 Completion: 2031
International Cooperative Growth Study (iNCGS) Post Marketing Surveillance Program for NutropinAq [Somatropin (rDNA Origin) Injection] NCT00455728	Status: recruiting Enrolment: 3000
The Influence of Growth Hormone (GH) Therapy on Short Stature Related Distress a Prospective Randomized Controlled Trial NCT01246219	Status: recruiting Enrolment: 120 Completion: December 2015
Long-term Phase IV Multicentre Study on the Safety and Efficacy of Omnitrope (rhGH) in Short Children Born Small for Gestational Age (SGA) NCT00537914	Status: ongoing, not recruiting Enrolment: 240 Completion: March 2021
A Phase III, Multi-centre, Randomised, Parallel Group Study of Safety and Efficacy of the LB03002 a New Sustained Release Formulation of Human Recombinant Growth Hormone as Compared to Standard Daily Therapy in Treatment Naive Children With Growth Failure Due to Insufficient Secretion of Endogenous Growth Hormone NCT00271518	Status: ongoing, not recruiting Enrolment: 144 Completion: December 2013
Cardiovascular Effects on Growth Hormone Replacement Therapy in Adults With Primary or Secondary Childhood Onset Growth Hormone Deficiency NCT01698944	Status: terminated due to low recruitment

Trial name and registration number	Details
A Multicenter, Open-label, Randomized Two Arm Cross Over Study Assessing Dyad (Subject and Caregiver) and Adult Subject Perception of Convenience and Preference of the Newly Developed Genotropin Mark VII Pen NCT01112865	Status: completed October 2011 Enrolment: 120 Results available
Assessment of the Ease of Use of Norditropin NordiFlex Relative to the One of the Device Previously Used by Patients or Parents NCT01245374	Status: completed April 2011 Enrolment: 103
Multicenter, Open-Label Study Assessing Dyad (Subject And Caregiver) Perception Of Convenience And Preference Of The Newly Developed Mark VII Injection Pen, Pfizer NCT00965484	Status: completed January 2010 Enrolment: 136
A Phase IV, Open Label, Multicenter, Case-controlled Study of Growth in Patients Using the Nutropin AQ Nuspin NCT01243892	Status: terminated due to slow enrolment
Effects of growth hormone treatment after final height in Prader-Willi Syndrome: a double-blind multicentre, cross-over study on the effects of growth hormone versus placebo on body composition and psychosocial behaviour in transition ISRCTN24648386	Status: completed 2011 Enrolment: 20

Additional information

European Medicines Agency (27 Feb 2012) Questions and answers on the review of somatropin-containing medicines. Outcome of procedures under Article 20 of Regulation (EC) No 726/2004 and Article 107 of Directive 2001/83/EC.

> *The European Medicines Agency has completed a review of the safety and effectiveness of somatropin-containing medicines, following the results of a French study* [Santé Adulte GH Enfant' (SAGhE)] *which suggested an increased risk of mortality in patients treated with somatropin compared with the general population. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of somatropin continue to outweigh its risks, but recommended changes to the product information to ensure that somatropin-containing medicines are used appropriately.*

U.S. Food and Drug Administration (4 Aug 2011) FDA Drug Safety Communication: Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death.

> *…did not provide evidence suggestive of a link between recombinant human growth hormone and an increased risk of death. Healthcare professionals and patients should continue to prescribe and use recombinant human growth hormone according to the labeled recommendations.*

Canadian Agency for Drugs and Technologies in Health (2012) Human Growth Hormone Treatment for Prader-Willi Syndrome in Adolescent and Adult Patients: Clinical Evidence, Safety, and Guidelines

References

Carel JC, Ecosse E, Landier F et al. (Feb. 2012) Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *Journal of Clinical Endocrinology & Metabolism.* 97 (2): 416-425.

Savendahl L, Maes M, Albertsson-Wikland K et al. (Feb. 2012) Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *Journal of Clinical Endocrinology & Metabolism.* 97 (2): E213-E217.

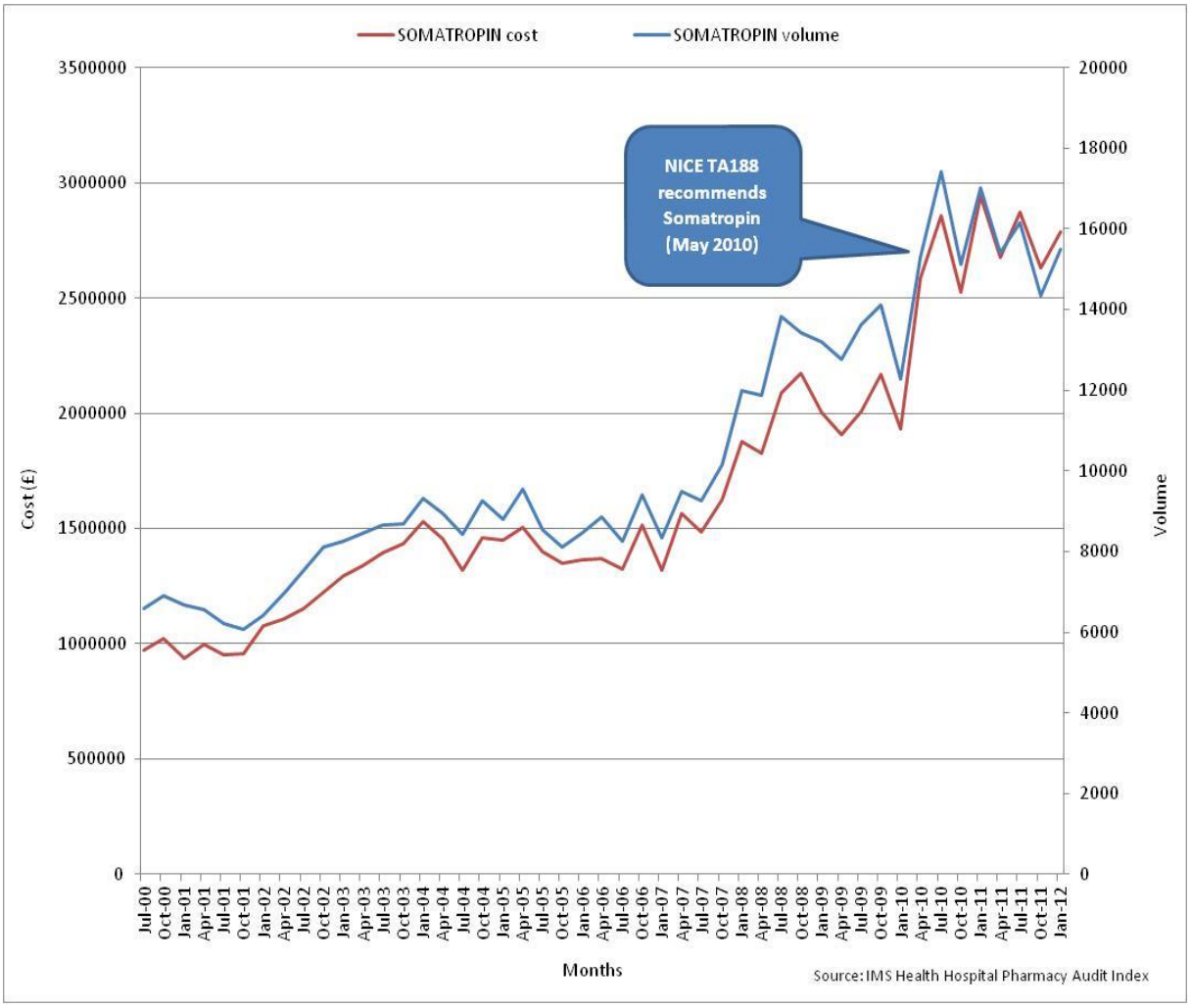
Appendix 3 – Implementation submission

1 Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of somatropin prescribed in hospitals in England between July 2000 and January 2012. These data need to be treated with caution as somatropin is prescribed for adults with growth failure as well as children, which these data do not account for.

Figure 1 Cost and volume of somatropin prescribed in hospitals in England

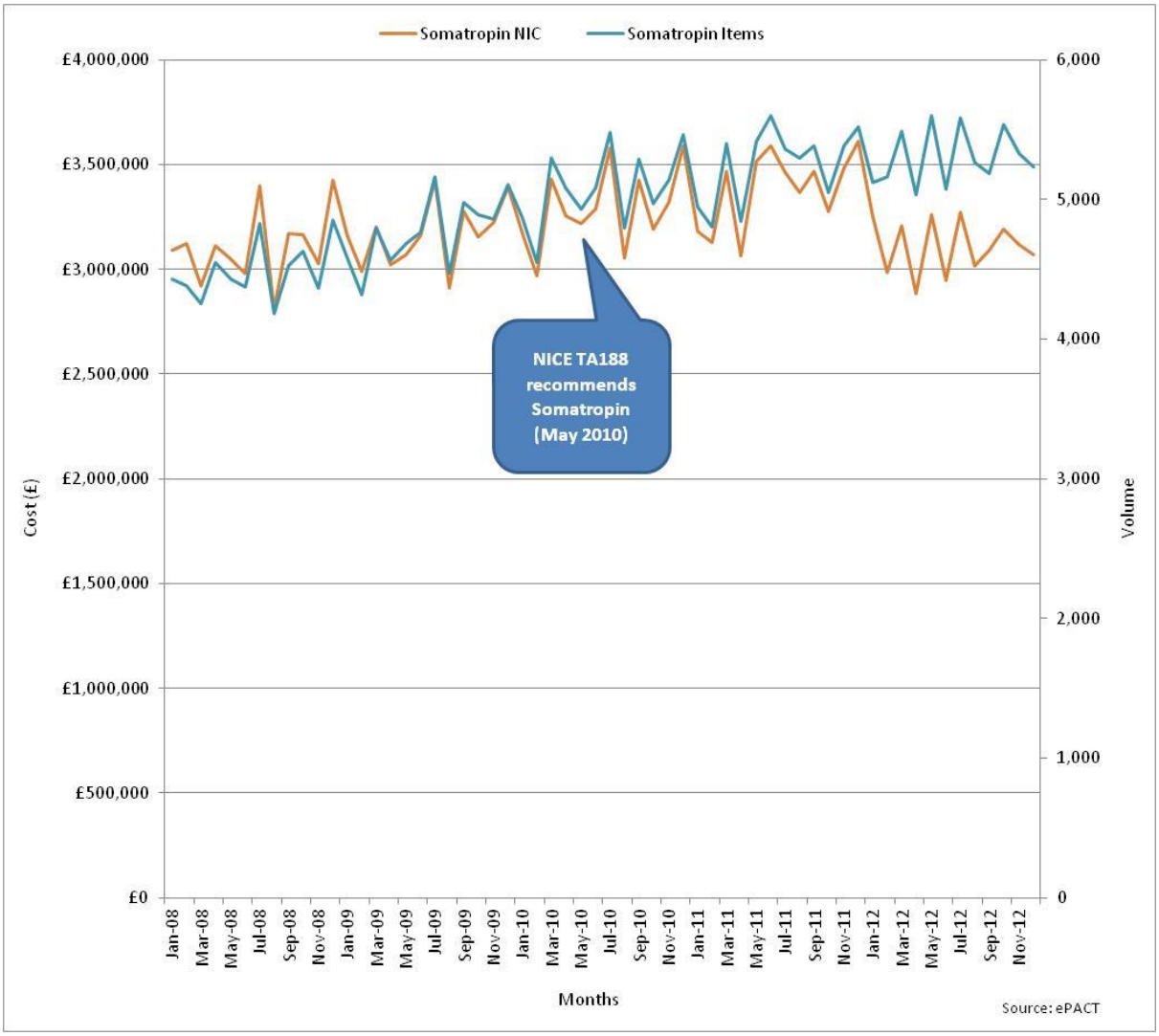


1.2 ePACT data

This section presents ePACT data on the net ingredient cost and volume of somatropin prescribed in primary care and in hospitals that has been dispensed in

the community in England between January 2008 and December 2012. These data need to be treated with caution as somatropin is prescribed for adults with growth failure as well as children, which these data do not account for.

Figure 2 Cost and volume of somatropin prescribed in primary care and in hospitals that has been dispensed in the community in England



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

Nothing to add at this time.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

Appendix A: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.