Comparison of growth hormone products and devices

Contents

Introduction 2
Available GH preparations 2
Available devices 3
Compliance/adherence in GH therapy 3
Patient preference for Devices / certain device characteristics 3
Device characteristics and effects on compliance 5
Product waste 6
Evidence on switching GH preparations 6

Summary

• There are currently seven preparations of somatropin (growth hormone) available in the UK. All are produced by recombinant DNA technology and have a sequence identical to that of human GH produced by the pituitary gland. According to the NICE guidance on use of growth hormone in children, there are no differences in the clinical effectiveness of the various somatropin products available.

• NICE guidance states that 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. In practice product choice will depend in part on the delivery system (device) and the support package offered by the manufacturer.

• There have been a number of advances in GH injection devices over the years addressing both usability and safety, and those currently available offer a range of different features. The importance of different features will vary between individuals, and many centres now offer a range of devices. Research has suggested that providing patients with a choice of device to suit their individual needs may improve adherence and patient satisfaction, and may therefore have an impact on the success of treatment.

• Although there have been a number of studies looking at patient preference when comparing a new device to an existing device, these are often manufacturer-sponsored, using the same brand of GH. A handful of studies comparing different devices available with different GH brands were located, but these are associated with various limitations and no firm conclusions can be made. The only one consistent finding is that there is an overall preference for products that do not require reconstitution.

• There appears to be no published evidence to suggest that the use of any particular device is directly associated with improved adherence/compliance compared to any other currently available on the market in the UK. Some of the data summarised in this report suggest that certain device features may improve compliance, but this is merely speculative and based on feedback from patients/carers rather than observation of actual behaviour in practice.

• There is limited published evidence on the effects of switching between GH preparations. One located paper describes a switch to Omnitrope® using a Dialogue Teamwork approach in a single centre in Sweden; this reported no impact on the children’s growth based on predicted growth trajectories. Pain at the injection site was reported commonly but attributed to the new injection device (new injection technique required).

• A US survey of clinicians exploring the effects of insurance-mandated brand switches during the course of paediatric GH therapy found that the majority reported no effects on efficacy or safety. Those who did most commonly raised concerns about treatment lapses, patient confusion, dosing errors, and side-effects (injection site pain). Negative patient-family reactions were also common, as could be expected from a switch that does not take into account patient/care preference or involve them in the decision-making process.
Introduction

Background
Growth hormone (GH) is an anabolic hormone secreted by the anterior lobe of the pituitary. It promotes growth of skeletal, muscular, and other tissues, and also has a role in the regulation of protein, lipid and carbohydrate metabolism. Secretion is pulsatile (occurring predominantly during deep sleep), reaches maximal levels during adolescence, and then declines with age (1, 2).

Somatropin (recombinant human GH) is currently the only active treatment option for growth failure in children with GH deficiency, Turner syndrome, chronic renal insufficiency (CRI), Prader-Willi syndrome (PWS), in short children born small for gestational age (SGA) and in children with short stature homeobox-containing gene (SHOX) deficiency. The place of somatropin in the treatment pathway depends on the child's particular condition and their age at diagnosis (1). The clinical management of GH deficiency in adults is also centred on replacement therapy with somatropin (3).

NICE guidance – children
NICE recommends somatropin as a treatment option for children with growth failure associated with any of the following conditions (1):

- GH deficiency
- Turner syndrome
- Prader–Willi syndrome
- chronic renal insufficiency
- born SGA with subsequent growth failure at 4 years of age or later
- SHOX deficiency.

Although this guidance was due for review in March 2013, it has now been moved to the static list, as 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 (4).

NICE guidance – adults
NICE recommends somatropin for the treatment of adults with GH deficiency only if they fulfil all three of the following criteria (3):

- 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.

A review of this guidance has been deferred until the results of a clinical trial are available (5).

Available GH preparations
There are currently seven preparations of somatropin available in the UK, all of which are produced by recombinant DNA technology, with a sequence identical to that of human growth hormone produced by the pituitary gland. The licensed indications, the available devices for these products and the add-on services are detailed in Tables 1-3. Although all somatropin products used to require some form of reconstitution prior to injection, several liquid formulations (supplied as ready-to-use solution) have since been developed and there are currently four brands available as a liquid formulation on the UK market (Norditropin®, NutropinAq®, Omnitrope®, Saizen®).

The cost of treatment with somatropin will depend on the dose. In children this is determined by their weight/body surface area, as well as the indication (1). In adults this will depend on the weight/size of the patient and their GH reserve (starting doses are around 0.2-0.5mg a day and maintenance doses seldom exceed 1mg per day) (3). As doses vary, costs per milligram (mg) have been presented in Tables 2 and 3 for comparative purposes.

All of the seven somatropin products currently available in the UK had been launched when the latest guidance from NICE on the use of GH in children was produced. The Appraisal Committee heard from clinical specialists and agreed that there appear to be no differences in the clinical effectiveness of the various somatropin products available. Although patient choice is an important factor in maximising adherence to therapy, there appear to be no specific features that determine which product a patient will choose. In practice the choice of product depends in part on the choice of delivery system and the support package offered by the manufacturer (1).
The guidance states that 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).

Focus of the review
Based on the NICE guidance and recommendations, it has been assumed that the available GH products are equal in terms of clinical effectiveness. The focus of this review was therefore to look at the following:

- The similarities and differences between the available GH brands and their associated devices
- Patient/carer preference for certain products/features (this has only considered studies that have compared the use of one device to another)
- Whether there is any evidence to suggest that any devices are associated with improvements in compliance
- Whether there is any evidence to suggest that switching patients between different GH brands is associated with patient harm

Available Devices
GH treatment regimens are likely to involve daily injections for many years, which can lead to problems with adherence. It is therefore essential that administration devices are convenient, easy and safe to use, and acceptable to patients (6).

GH treatment was originally administered using conventional needles and syringes, and subsequent advances in delivery have focused mainly on the development of injection devices that simplify the process and improve tolerability. Reusable pen devices were introduced in the 1990s and these became the ‘gold standard’, with most patients preferring their use over conventional needles and syringes. Needle guards that automatically cover the needle before and after injection have also been designed to improve the safety of injection pens; they also address the observation that patients may prefer not to see a needle. As patients may report less pain if they do not have to make the injection themselves, newer devices offering automatic needle insertion, auto-injection and needle-free injection have also been developed. Needle-free devices are also available; these expel the GH at high pressure through a small nozzle, forcing it through the skin to be dispersed in subcutaneous layers (7).

In recent years the number of GH injection delivery devices on the market has expanded, increasing the choice available to patients (8). Those currently available in the UK and their features are outlined in Tables 2 and 3.

Historically, injection devices were chosen on behalf of the patient by medical and nursing staff, but in recent years many endocrinology centres have moved away from this practice and offer some form of patient choice upon initiation of therapy, with larger centres generally offering a range of devices (9). Research has suggested that providing patients with a choice of device to suit their individual needs may improve adherence and patient satisfaction, and may therefore have an impact on the success of the treatment (8-10).

Compliance/adherence in GH therapy
A recently published systematic review of the literature on adherence to paediatric GH therapy [number of included studies not stated] reports that estimates of the prevalence of non-adherence have varied widely (5-82%), depending on definitions and methods used. A study of the easypod device (n=824), which records dose history and allows for objective measurement of adherence, reported an adherence rate of 87.5% over a 3-month period (11).

Barriers to adherence may include scheduling issues (social convenience), cognitive/emotional issues, as well as medication issues (9). These may include lack of responsibility for treatment (adolescent patients), underestimating the importance of missing doses, injection discomfort, dissatisfaction with the results of treatment, and inadequate contact with the healthcare provider (8). Specific medication-related factors associated with poor adherence to GH therapy in observational studies have included lack of choice of injection device, use of a conventional syringe rather than a pen device, discomfort with injections, and lack of home delivery with hospital tracking (among others) (9). Therefore while patient information and education may improve concordance, injection device characteristics may also play a role (8).

Patient preference for devices/certain device characteristics
A survey of physicians, nurses, teenage self-injecting patients, and parents injecting their children (aged <14 years) (n=67) found that the most important features of a device were reliability, ease of use, lack of pain during injection, safety in use and storage, and the number of steps in preparation before use, during use and after (12).
A prospective single-centre study in the UK (n=125) examining the factors determining patient choice of GH device reported that 46% chose a needle-free device and the remainder a pen device (many with needle and syringe devices for holidays); no baseline factors were found to predict which device was chosen. The most common factors that the patients/carers gave for choosing a particular device included ease of use, and whether it was needle-free. Other less important factors were needle-related (needle guard, needle autoinsertion), feel, appearance and action of the device. Different patients however had different priorities (for example some were chosen as they were quiet when others were chosen as they were considered loud) (13). Another study looking at patients’ and parents’ choices of administration device found that the option of a needle-free device was rated only ninth in the decision criteria, with the most important factors influencing device choice being lack of bruising and whether it was an autoinjector (14).

As can be seen by the above examples, the results of this type of study have varied. It is therefore difficult to class certain features as particularly advantageous or disadvantageous, as this appears to vary between patients.

There have been a number of studies looking at patient preference when comparing a new device to an existing device – these are often manufacturer-sponsored, using the same brand of GH and evaluating a device that is new to the market. Although these studies may provide information on the acceptability of newer devices being introduced to the market, they do not provide any comparison of acceptability of devices available for different brands of GH, which would be more valuable when considering potential cost savings in practice. Some examples of these studies have however been summarised below for information (they may provide some indication of what features [introduced by the new devices] patients consider more advantageous).

A study comparing the ease of use and preference for a disposable Genotropin® pen compared to a reusable Genotropin® pen (in patients previously using the reusable pen) reported that 59.8% of 133 analysed patient-caregiver dyads preferred the disposable pen to the reusable pen, 63.2% saying that it was easier to use. Most features of both pens were associated with high ease-of-use ratings. Although activities associated with pen preparation (mixing the medicine; removing air bubbles; remembering the dose) were considered by some to be easier with the disposable pen, up to half found no difference between the two devices. In addition over 50% found no difference between the two pens with regards to needle attachment and storage (15).

A randomised crossover study (n=67) comparing a liquid formulation of GH (Norditropin® SimpleXx®) to a older freeze-dried product requiring constitution (Norditropin® PenSet [not marketed in the UK]) found that there was an overall preference for the liquid product, with 64% rating it as easier to inject and 98% rating the system as easier to use overall. Elimination of the reconstitution procedure and simplification of the cartridge changing procedure also enabled younger children to use it. Although 93% of patients/carers did not think that use of the SimpleXx® cartridge would improve compliance, all had been using the PenSet prior to the study and so had already become familiar with this device (16).

Preference for the liquid SimpleXx® formulation was also shown in a study which switched 36 patients who had previously used the powder for reconstitution. A total of 85% found the liquid preparation to be more convenient to use, 88% felt that handling of the device was easier, and 79% overall preferred the new system (17). A further study (n=103) switched patients on a number of previous brands of GH (all powder for reconstitution) to Norditropin® SimpleXx® and reported a 92% rate of preference for the liquid preparation, irrespective of the previous therapy used, mainly due to the lack of reconstitution required. The majority of patients (84%) had however already been fairly or very satisfied with the system they were using before the switch (18).

A handling study conducted in the UK (n=25) found that NordiPen® and NordiPenMate® (auto-inject accessory) was considered convenient and easy to use, compared to other pen systems. Whereas parents tended to prefer NordiPenMate® (made it easier for them to inject their children), children performing the injections themselves preferred NordiPen®, as they liked to be in control of the injection procedure (15). Another open-label, uncontrolled study in which patients (n = 50; age range 4-17 years) using Norditropin NordiFlex without NordiFlex PenMate were trained to use the FlexPro/FlexPro PenMate and NordiFlex/NordiFlex PenMate systems found that 46% of those using the NordiFlex/NordiFlex PenMate found it helped to reduce the anxiety associated with injection, and 30% thought that significantly impacted on the pain associated with injection (19).

An open-label uncontrolled study sought opinions on the easypod autoinjection device from users of other Saizen devices (n=2 cool.click and n=54 one.click) or treatment-naïve patients (n=5). The majority (98%) reported a ‘good’ or ‘very good’ overall impression of the device; the pre-programmed dose feature was considered useful or very useful by all.
Comparison of growth hormone products and devices

The skin sensor, on-screen instructions, display of remaining dose, confirmation of injected dose, and automatic needle attachment were considered ‘very useful’ by the majority. Most of the positive comments focused on the ease of use, whereas most of the negative comments concerned the size of the device. After 2 months, 87% said they would prefer to continue with this device over the other Saizen® devices (20).

Two located studies provide some comparison of patient acceptance for devices available with different brands, but detail is lacking (one was a letter to the editor; the other a meeting abstract). In the first, Nordipen® (liquid GH preparation; presumably SimpleXx cartridges) was compared to Humatrope® (HumatroPen®), Genotropin® (GenotroPen®) and NutropinAf® in a crossover study (2 weeks of Nordipen® and then two weeks of one of the other products in a randomised fashion). Of note the letter states that the NutropinAf® was given via syringe, whereas there is now a pen device available (so the results for this would not be relevant in current clinical practice). In addition a new Humatrope® pen was launched in 2010 and therefore this is likely to be an older device that is no longer in use. Overall 77% of patients preferred Nordipen® to HumatroPen®, 71% preferred it to Genotropin® and 94% to NutropinAf®. Respective results for parents were 97%, 81% and 89%. Nordipen® was preferred by most parents with respect to ease of preparation (73%), ease of measuring doses (60%), and ease of administration (76%) (21).

The second was a post-hoc analysis of a survey, reported at conference. The results of this suggest that a lower number of patients using Norditropin FlexPro® (not currently available in the UK) or Norditropin NordiFlex® experienced pain and/or stinging compared to other GH products (the exact ones that it was compared to were not specified). This association remained despite adjustment for device type. Of note however, 234 of the 295 participants were proxies for patients, and the influence of caregivers responding as proxies for patients warrants further investigation (22).

A survey conducted to determine the most important attributes of a GH administration device (discussed above) also asked participants how they rated the existing devices for each of these attributes (11). The devices were grouped together according to type (prefilled syringe, injector pens or needle-free devices); results for individual brands are not reported. Pre-filled syringes and autoinjector pens were generally considered to be reliable (mean score of 8.6-9.3 out of 10) and easy to use, whereas needle-free devices were rated as having low reliability (mean 2.0) and as moderately easy to use. All device types were rated as having similar levels of pain (mean score of 6-7). Conclusions are however limited as only 4 patients had previous experience of a needle-free device and 6 had previous experience of prefilled syringes (compared to 48 with injector pens).

A further small study suggested that use of an automatic injection device may improve adherence, with 82% preferring its use as it was considered to be less painful and the child did not see the needle or need to insert the needle manually. It was however a very small study (n=14) and it compared two products no longer in use in the UK (KabiVial/Auto Injector versus KabiPen 16 IU/ml) (23). The same finding was however reported in a later study comparing two prototype pens that differed only with respect to needle insertion (automatic or manual). The authors concluded by their observations that pain during GH injection can be diminished by automatic needle insertion (24).

Finally, a simulated time-and-motion analysis involving six nurses who were naive to GH administration that compared Norditropin® NordiFlex (NNF) and Norditropin® NordiPen (NNP) (both liquid formulations) to Genotropin® Pen (GTP) and HumatroPen® (HTP) (both requiring reconstitution) suggested that use of Norditropin® products was associated with less total time (25). This was mainly attributed to a shorter amount of time needed to learn (15.8 minutes for NNF, 16.2 for NNP, 26.0 for GTP and 24.0 for HTP) and new package preparation times (1.35, 2.48, 4.11, and 8.64 minutes, respectively). The results of the latter are not surprising in light of the requirement for reconstitution for GTP and HTP, and the results for the preparation of the second dose reflect this, as they were much faster (0.86, 0.92, 1.30, and 0.94 minutes, respectively). Once prepared for use, there were no significant differences in administration time between the difference devices. Also the nurses became more efficient in performing each step with practice, so any observed differences are likely become smaller over time, as the user becomes familiar with the devices. The number of steps required to prepare the devices was higher with GTP and HTP, again as would be expected due to the reconstitution processes involved.

Device characteristics and effects on compliance

Although the studies outlined above help to identify devices/device features that are rated as easier to use/ more preferable by a majority of patients/ caregivers, there is variation between patients. In addition they do not measure compliance directly, so any association with improved compliance is merely speculative.
A search of the published literature failed to locate any published evidence to show that the use of any particular device is directly associated with improved adherence/compliance compared to any other currently available on the market in the UK. One study actually reported that there were no significant differences in concordance or height velocity according to type of GH device; the study was however small (46 children), devices were grouped together (automatic injection devices; manual injection pen devices; needle-free injection devices), and only small numbers used the needle-free device (so the conclusions that can be drawn are limited) (10).

An analysis of data from the GHMonitor database (register of children in North America treated with the Saizen® brand) compared patients treated with the cool.click needle-free device to those treated with the traditional needle and syringe [no longer used in practice], and reported no difference in response over 2 years of treatment; however more patients treated with the needle and syringe missed over half of their prescribed dose (13.4% v 6%; p=0.002). Compliance was however based on pharmacy over half of their prescribed dose (13.4% v 6%; p=0.002). Compliance was however based on pharmacy report of the number of doses missed, and factors influencing compliance (e.g. training in technique and follow-up) were not controlled for. Significantly lower growth was identified among patients missing over 15 injections per month compared to those missing fewer injections (6.3cm v 9.4cm per year)(26).

**Product waste**

Although the results of a laboratory-based study used to inform a modelling-based analysis suggested that there may be differences between Norditropin® devices and the Omnitrope Pen 5® (favouring the former) in terms of product waste during dose setting and prior to injection, no evidence of this being a significant issue associated with use in clinical practice was located (27).

**Evidence on switching GH preparations**

Overall there is little published information on switching between GH products. Only one study evaluating the effects of a switch to biosimilar (Omnitrope®) in clinical practice was located – this found that switching did not impact on growth trajectory. This and other located data of relevance are summarised below.

Flodmark et al describe the outcomes of a treatment plan implemented at Skane University Hospital in Sweden in 2009, which involved switching children requiring GH treatment from originator GH products to the biosimilar Omnitrope®, using a Dialogue Teamwork approach (28). A total of 102 children were offered the switch (98 accepted); those that weren’t (n=18) had an expected duration of further treatment of <6 months or a history of allergic reaction to other GH preparations. All patients or their parents were provided with information/support to aid their decision, including for example a letter describing the rationale for the switch, the opportunity to discuss it with the physician responsible for their care, and a visit to a specialist endocrinology nurse for instructions on how to use the device. No additional specific visits, tests or assessments were required as part of the study and routine clinical care continued.

A model was used to predict individual growth trajectories, based on growth data obtained before the switch to Omnitrope® occurred. This prediction was then compared to the actual observed height after the switch. The results indicated that the switch did not have any impact on growth velocity in patients overall, or in specific growth disturbances. The standard deviation of differences between predicted and observed values was 1.9cm (i.e. 90% of the predicted values are expected to lie within 3cm of the values actually observed). A total of 19 adverse drug reactions were reported in the 12 months following the switch; 18 of these were pain at the injection site (6 switched back to the original GH product). The authors say that the reporting of injection pain can at least in part be explained by the use of a new injection device, which means that patients must learn and become accustomed to a new injection technique; this is reinforced by the fact that 12 patients experiencing pain continued on Omnitrope® following provision of advice and education on injection technique.

The authors conclude that the switch to Omnitrope® had no impact on the children’s growth and provided substantial cost savings. Based on their results, and on the Dialogue Teamwork approach used to implement the switch, they propose that the following four elements are critical to the success of such an approach:

- Patients should be provided with clear information about the reasons for the change;
- Individual patients/carers should be given sufficient opportunities to discuss the change with the different healthcare professionals involved;
- There should be a joint team approach that avoids mixed messages from the different healthcare professionals involved;
- Patients should be provided with reassurance and personal support throughout the change.
An earlier conversion program was introduced in a health maintenance organisation in the US (HIP-NY) in 2004, and this saw patients converted from their current GH product to Norditropin® (chosen because it was believed that the services offered by the manufacturer were superior to those offered by others at the time). This did not however report the patient outcomes or satisfaction after switching, rather the process and success in terms of market share, and therefore this has not been considered here any further (29).

Two US surveys have focused on physician attitudes or the potential administration burden on clinics associated with switching GH products. The first was mailed to 800 paediatric endocrinologists (response rate of 29%) in the US, to assess opinions on the interchangeability of human GH products (30). The majority (92%) of respondents considered all GH products to be equivalent, but just under half of these (44%) favoured limiting a formula to one brand. Those who did not consider this to be appropriate most commonly cited factors such as hindering of competition and lack of freedom of choice as reasons; other factors considered included differences in drug delivery systems and different extents of manufacturer support. The physicians expressed a general objection to switching products, especially if the patient was responding to therapy and tolerating the product well; most would not consider switching unless patients were having problems with the product (e.g. inability to reconstitute).

The second survey explored the effects of insurance-mandated brand switches during the course of paediatric GH therapy on clinical practice. A total 812 members of the Pediatric Endocrine Society were emailed the survey and 231 (28%) responded. The majority of respondents (90%) had switched GH brands in their patients at least once and 50% had experienced multiple switches. Switching occurred to each of the commercially available GH products available at the time, and most often occurred between innovator products. Three of the nine survey questions explored potential adverse effects of switching – free text comments were supplied and a set of standardised code words or phrases were developed from these. Overall 92% reported no effects on efficacy and 87% reported no safety concerns. Of the 15 patients who ticked ‘yes’ to experiencing effects of switching on efficacy, the majority related this to decreased adherence from lapses in treatment, confusion, and errors associated with a new device. Only a few reported reduced growth velocity but no further information on this is included in the report. Of the 24 who ticked ‘yes’ to having safety concerns, those most frequently reported included dosing errors, treatment lapses due to having to learn how to use a new device, and patient confusion related to different GH concentrations in various products [although all products in the UK are now dosed in mg so this would presumably no longer be an issue]. The majority of respondents (66%) reported negative patient-family reactions when brand or device preferences were ignored by insurance-mandated switches, with concerns raised about having to learn to use a new product and the effects of this on treatment. Switching was also associated with extra physician time for patient counselling and reassurance, and paperwork (31). This study had a low response rate and therefore non-response bias cannot be ruled out. In addition it was exploratory, and no conclusions about the prevalence or magnitude of the reported findings can be made. The results are based on an insurance-mandated switch process (rather than rationalising product range) – this would not take into account patient preference for a particular type of device and would not involve the patient/carer in device selection; this itself is likely to lead to poorer adherence and outcomes, as identified in other research.

Ebbers et al reviewed the scientific literature to determine whether switching between biopharmaceuticals may compromise patient safety, with a focus on products for which biosimilars are available (32). Both studies describing switches between innovators and those describing switches between innovators and biosimilars were included, if safety was reported. A total of 13 crossover studies (n=415) comparing GH products were included, and none of these reported any adverse effects attributable to switching. The studies were however mainly geared towards assessment of efficacy (and underpowered to detect significant changes in the safety profile), and generally too short to allow determination of possible long-term side-effects of switching. The authors also analysed data from the EudraVigilance adverse reaction database, and failed to locate any reports for biosimilars that were possibly related to switching (although there is currently no appropriate coding for adverse events resulting from switching). Although the study did not identify any evidence to suggest that the process of switching between biopharmaceuticals poses any risk to patients, it is not possible to definitively conclude a lack of risk due to the limitations of the currently available data. The authors go on to discuss some of the reasons why switching between biopharmaceuticals should be done prudently, including possible differences in potency (titration may be required), patient anxiety, and the need for increased staff time on device teaching and patient reassurance.
Romer et al analysed data from three Phase III studies to assess the efficacy and safety of Omnitrope® in children switching to Omnitrope® after 9 months of Genotropin®, compared with those using continuous Omnitrope® only (33). The authors report no differences between the groups in terms of height or height velocity, and modelling data (where growth was predicted based on data observed during 9 months of Genotropin® and compared to actual observed growth) showed that most data points for those treated with Omnitrope® fell within the defined limits of the prediction model. There was no discernible difference in adverse drug reactions, with the majority reported during the first 9 months of treatment (regardless of which GH product was used), and the switch did not appear to increase the risk of immunogenicity (only 3 patients overall developed anti-GH antibodies during 18 months). The authors note that the results are based on a post-hoc analysis (as the original studies were designed to demonstrate that Omnitrope® has a similar safety and efficacy profile to Genotropin®, not to look at switching). Other limitations included the limited period of observation (9 months before and after switching therapy), and the lack of information on adherence before and after the switch.
Table 1: Licensed indications of the growth hormone products available in the UK

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotropin® (Pharmacia)</th>
<th>Humatrope® (Lilly)</th>
<th>Norditropin® (Novo Nordisk)</th>
<th>NutropinAq® (Ipsen)</th>
<th>Omnitrope® (Sandoz)</th>
<th>Saizen® (Merck Serono)</th>
<th>Zomacton® (Ferring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHD adults</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GHD children</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>✓</td>
<td>x¹</td>
<td>x*</td>
<td>x¹</td>
<td>✓</td>
<td>x¹</td>
<td>x</td>
</tr>
<tr>
<td>Growth disturbance in SGA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>SHOX deficiency</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

1. unless also have a diagnosis of growth hormone deficiency
2. In perpubertal children
* not clear from SPC
Table 2: At-a-glance comparison of the main device characteristics and basic prices

<table>
<thead>
<tr>
<th>Brand and devices</th>
<th>Liquid formulation</th>
<th>Room temp. stable</th>
<th>Prefilled</th>
<th>Auto-injection</th>
<th>Dose preset</th>
<th>Needle guard/cover</th>
<th>Dial back</th>
<th>H/C</th>
<th>Home nurse visits</th>
<th>Website</th>
<th>helpline</th>
<th>Cost per mg excl VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£17.39</td>
</tr>
<tr>
<td>Genotropin® Pen</td>
<td>x #</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GoQuick®</td>
<td>x #</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>£17.39</td>
</tr>
<tr>
<td>MiniQuick®</td>
<td>x #</td>
<td>✓+</td>
<td>✓</td>
<td>x</td>
<td>N/A</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humatrope®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£18.00</td>
</tr>
<tr>
<td>HumatroPen®</td>
<td>x ~</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norditropin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£21.27</td>
</tr>
<tr>
<td>NordiPen®</td>
<td>✓</td>
<td>✓^</td>
<td>x</td>
<td>✓^</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NordiFlex®</td>
<td>✓</td>
<td>✓^</td>
<td>✓</td>
<td>✓^</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NutropinAq®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£23.18</td>
</tr>
<tr>
<td>NutropinAq® Pen</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnitrope® (biosimilar)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£17.35</td>
</tr>
<tr>
<td>SurePal™</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnitrope Pen®</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saizen®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£23.18</td>
</tr>
<tr>
<td>easypod®</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one.click®</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomacton®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£19.92</td>
</tr>
<tr>
<td>ZomaJet VisionX®</td>
<td>x ~</td>
<td>x</td>
<td>x</td>
<td>N/A</td>
<td>x</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Reconstitution within the device (2-chamber cartridge); ~ - diluent supplied separately; + can be kept at room temp for ≤6 months before use; *can be kept at room temp for ≤3 weeks after first use; ^if PenMate® auto-inject accessory or NovoFine® Autocover® needle used; a the dose can still be changed without any wastage of the product if you dial above the correct dose, but reset is required
### Table 3: Characteristics of the growth hormone devices available in the UK

<table>
<thead>
<tr>
<th>Devices</th>
<th>Strengths (increments)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Price per mg (-VAT)</th>
<th>Add-ons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotropin®</strong>&lt;br&gt;(for use with Genotropin® cartridges)</td>
<td>5.3mg cartridge (increments of 0.1mg)&lt;br&gt;12mg cartridge (increments of 0.2mg)</td>
<td>• Clear digital dose display&lt;br&gt;• Optional needle guard&lt;br&gt;• Pen can be personalised (GenoCaps®)&lt;br&gt;• Dial back possible&lt;br&gt;• May be stored at room temperature (≤25°C) for up to one month prior to reconstitution</td>
<td>• Cartridge needs to be inserted into the device (not prefilled)&lt;br&gt;• Reconstitution required (2-chamber cartridge)&lt;br&gt;• Needs to be stored in the fridge after reconstitution&lt;br&gt;• Dose cannot be preset</td>
<td>£17.39</td>
<td><strong>Add-ons</strong>&lt;br&gt;Patient support programme overseen by homecare company (includes nurse-led patient education; clinical waste collection, adherence monitoring, SMS reminder service)&lt;br&gt;Helpline (8.30am to 5pm; available out of hours for emergencies)&lt;br&gt;Website for patients and healthcare professionals <a href="http://www.genotropin.co.uk/">http://www.genotropin.co.uk/</a>&lt;br&gt;Range of educational and patient support materials provided at initiation of therapy</td>
</tr>
<tr>
<td><strong>GoQuick®</strong> - prefilled multi-dose disposable pen</td>
<td>5.3mg cartridge (increments of 0.05mg)&lt;br&gt;12mg cartridge (increments of 0.15mg)</td>
<td>• Prefilled with cartridge (disposable)&lt;br&gt;• The dose can be preset&lt;br&gt;• Optional needle guard&lt;br&gt;• Dial back possible&lt;br&gt;• May be stored at room temperature (≤25°C) for up to one month prior to reconstitution</td>
<td>• Reconstitution required (2-chamber cartridge)&lt;br&gt;• Needs to be stored in the fridge after reconstitution</td>
<td><strong>MiniQuick® injection</strong> - single-dose daily disposable syringe</td>
<td>0.2-2mg doses available (in 0.2mg increments)</td>
</tr>
<tr>
<td><strong>Humatrope®</strong>&lt;br&gt;(for use with Humatrope® cartridges)</td>
<td>6mg cartridge (0.025mg increments)&lt;br&gt;12mg cartridge (0.05mg increments)&lt;br&gt;24mg cartridge (0.1mg increments)</td>
<td>• Optional needle guard&lt;br&gt;• Dial back possible</td>
<td>• Cartridge needs to be inserted into the device (not prefilled)&lt;br&gt;• Reconstitution required (the cartridge needs to be reconstituted with the diluent, which is supplied separately, before being inserted into the device)&lt;br&gt;• Needs to be stored in the fridge before and after reconstitution&lt;br&gt;• Dose cannot be preset</td>
<td>£18.00</td>
<td><strong>Add-ons</strong>&lt;br&gt;Patient support programme overseen by homecare company (includes nurse-led patient education; clinical waste collection, and SMS delivery reminder service). Adherence monitoring is currently being evaluated.&lt;br&gt;24-hour Lilly device line for patients and HCP&lt;br&gt;Range of educational and patient support materials provided at initiation of therapy</td>
</tr>
</tbody>
</table>
### Table 3: continued

<table>
<thead>
<tr>
<th>Devices</th>
<th>Strengths (increments)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Price per mg (-VAT)</th>
<th>Add-ons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norditropin®</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NordiPen® (for use with SimpleXx® cartridges)</td>
<td>5mg cartridge (0.05mg increments)</td>
<td>• Premixed solution</td>
<td>• Cartridge needs to be inserted into the device (not prefilled)</td>
<td>£21.27</td>
<td>Patient support programme (Nordicare®) overseen by homecare company</td>
</tr>
<tr>
<td></td>
<td>10mg cartridge (0.1mg increments)</td>
<td>• Can be kept at room temperature (below 25°C) for up to 3 weeks after first use</td>
<td>• If you dial above the correct dose, the dose selector needs to be reset</td>
<td></td>
<td>(endocrine specialist nurses deliver a tailored nursing service; includes nurse-led patient education; clinical waste collection, adherence monitoring, SMS reminder service)</td>
</tr>
<tr>
<td></td>
<td>15mg cartridge (0.1mg increments)</td>
<td>• NordiPenMate® auto-inject accessory available</td>
<td>• No needle guard on the device; although the NovoFine® Auto-cover® needle can be used (also the needle will be hidden if NordiPenMate® is used)</td>
<td></td>
<td>24-hour nurse support helpline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Graphic and classic designs available</td>
<td>• Dose cannot be preset</td>
<td></td>
<td>Range of educational and patient support materials provided at initiation of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NordiFlex® prefilled multidose disposable injection pen</strong></td>
<td>Only 15mg size available in the UK (increments of 0.075mg)</td>
<td>• Prefilled device</td>
<td>• No needle guard on the device; although the NovoFine® Auto-cover® needle can be used (also the needle will be hidden if NordiFlex PenMate® is used)</td>
<td>£23.18</td>
<td>General information on GH therapy available via <a href="http://www.novonordisk.co.uk">www.novonordisk.co.uk</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Premixed solution</td>
<td>• Dose cannot be preset</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can be kept at room temperature (below 25°C) for up to 3 weeks after first use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NordiFlex PenMate® auto-inject accessory available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dial back possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NutropinAq® Pen</strong></td>
<td>Only 10mg size available in the UK (0.1mg increments)</td>
<td>• Premixed solution</td>
<td>• Cartridge needs to be inserted into the device (not prefilled)</td>
<td>£20.30</td>
<td>Patient support programme overseen by the homecare company (includes nurse-led patient education; clinical waste collection, adherence monitoring)</td>
</tr>
<tr>
<td>(for use with NutropinAq® cartridges)</td>
<td></td>
<td>• LCD display</td>
<td>• Needs to be stored in the fridge before and after first use</td>
<td></td>
<td>App for patients, incorporating dose alarms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dial back possible</td>
<td>• Dose cannot be preset</td>
<td></td>
<td>Patient support helpline 8am-7pm; nursing team take out of hours calls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Optional needle shield</td>
<td></td>
<td></td>
<td>Range of educational and patient support materials provided at initiation of therapy</td>
</tr>
<tr>
<td>Devices</td>
<td>Strengths (increments)</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Price per mg (-VAT)</td>
<td>Add-ons</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Omnitrope®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SurePal™ pen device (for use with Omnitrope cartridges for SurePal™)</td>
<td>5mg (0.05mg increments) and 10mg (0.1mg increments)</td>
<td>• Premixed solution (no reconstitution required) &lt;br&gt;• Dose can be preset &lt;br&gt;• Needle is hidden throughout use &lt;br&gt;• No priming is required &lt;br&gt;• Cartridges are dose-specific and will not fit in the incorrect pen</td>
<td>• Cartridge needs to be inserted into the device (not prefilled) &lt;br&gt;• Needs to be stored in the fridge before and after first use &lt;br&gt;• Dial-back not possible; although reset process is simple and will avoid waste</td>
<td>£17.35</td>
<td>Patient support programme overseen by the homecare company (includes nurse-led patient education, clinical waste collection, adherence monitoring) &lt;br&gt;Helpline (opening hours vary depending on homecare company) &lt;br&gt;Online support available – personal page that can be customised; includes options to record when doses administered, set SMS reminders, etc &lt;br&gt;Range of educational and patient support materials given at initiation of therapy and available via the website</td>
</tr>
<tr>
<td>Omnitrope Pen®™ (for use with Omnitrope Pen cartridges)</td>
<td>5mg (0.05mg increments) and 10mg (0.1mg increments)</td>
<td>• Premixed solution (no reconstitution required) &lt;br&gt;• Needle guard</td>
<td>• Cartridge needs to be inserted into the device (not prefilled) &lt;br&gt;• Needs to be stored in the fridge before and after first use &lt;br&gt;• Dial-back not possible (it needs to be reset otherwise there will be drug wastage) &lt;br&gt;• Dose cannot be preset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>easypod® autoinjector #</td>
<td>6mg, 12mg and 20mg liquid cartridges (all 0.01mg increments)</td>
<td>• Automatically injects and delivers dose &lt;br&gt;• Dose is preset by HCP (protected by PIN code) &lt;br&gt;• Records dose history; dose log allows adherence monitoring &lt;br&gt;• Needle hidden throughout use &lt;br&gt;• On-screen instructions for user &lt;br&gt;• Audible and visual signals show when the dose is complete &lt;br&gt;• Can control ‘comfort parameters’ (e.g. injection depth/time, needle speed) &lt;br&gt;• Device can be personalised (on screen name; facias) &lt;br&gt;• Dose adjustment function to minimise waste (set by HCP) &lt;br&gt;• Skin sensor to ensure correct placement &lt;br&gt;• Premixed solution</td>
<td>• Cartridge needs to be loaded into the device &lt;br&gt;• Batteries need to be replaced approx. once every year &lt;br&gt;• Relatively large device &lt;br&gt;• Needs to be stored in the fridge before and after first use &lt;br&gt;• Electronic device – requires care during storage and use</td>
<td>£23.18</td>
<td>‘My Support’ programme co-ordinated through homecare company and delivered by dedicated nurse team (includes nurse-led patient education and regular follow-up, clinical waste collection) &lt;br&gt;Adherence monitoring through dose history recorded on the device (can be sent to HCP) &lt;br&gt;My Support website, and helpline support available 9am to 9pm, 365 days/year &lt;br&gt;Range of educational and patient support materials provided at initiation of therapy</td>
</tr>
<tr>
<td>Devices</td>
<td>Strengths (increments)</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Price per mg (-VAT)</td>
<td>Add-ons</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Zomacton®                    | Click easy (8mg) powder for reconstitution | • Automatic needle insertion and dose delivery  
• Injection depth may be varied (2-8mm)  
• click easy vials may be stored at room temp prior to reconstitution  
• Dial back possible | • Reconstitution required (using the click easy reconstitution device)  
• Needs to be stored in the fridge during use  
• Dose cannot be preset  
• The device requires activation  
• Dose is set in number of clicks (0.12mg each click) rather than mg as with other available devices | £19.92               | As above                                                                 |
| one.click® autoinjector * * * | Click easy (8mg) powder for reconstitution Dosed in 0.12mg increments | • Needle-free  
• No product wastage  
• Dial back possible  
• Does not require daily needle change (head needs to be changed every 7 days)  
• Audible sound with each dose (may be a disadvantage for some)  
• Automatic locking system after dose given | • Reconstitution required (using the click easy reconstitution device)  
• Needs to be stored in the fridge during use  
• Dose cannot be preset  
• The device requires activation  
• Dose is set in number of clicks (0.12mg each click) rather than mg as with other available devices | £23.18               | As above                                                                 |

**Key:** GHD – growth hormone deficiency; CRI – chronic renal insufficiency; SGA – small for gestational age; PWS - Prader-Willi syndrome; dial back – the dial can be simply turned back to the correct dose, if this is missed when dialling, without product waste. *Genotropin Mixer® is available still in the UK but not commonly used so this has not been discussed. **The Omnitrope Pen (5 and 10) will be phased out over time following the launch of the SurePal™ pen device. ***easypod is the only Saizen device currently marketed in the UK (the other product has however been included for information). +ZomaJet 2® Vision needle-free device (for use with the 4mg vial) is no longer actively marketed and has therefore not been discussed. #Although the easypod can take both the click.easy (powder for reconstitution) and the Saizen ready to use liquid cartridges, this table assumes use of the latter.

**Add-ons:** This table provides a summary of the ‘add-ons’ available for each GH product. Please note that the exact specifications of homecare/patient support services offered vary. The provision of further detail of this aspect is however outside the scope of the review and the relevant manufacturers should be contacted for further details, if required.
References

2. Martindale
3. Growth hormone deficiency (adults) - human growth hormone (TA64; August 2003) http://www.nice.org.uk/guidance/TA64
22. Divino V et al (2012) Norditropin pen users may experience less pain & stinging upon injection compared with other rhGH products. Endocrine Reviews; 33/3 (Meeting Abstracts)
29. Kaufman MB, Brodin KA, Sarafian A (2006) A growth hormone conversion program and patient outcomes at a not-for-profit HMO. Formulary; 41:82-90