Thank you to all Australians who supported the submission to the PBAC for Human Growth Hormone to be listed for subsidy for adults requiring replacement. The submission was considered and rejected at the July meeting in 2011. The APF and its members have been deeply involved in supporting the application, and are extremely disappointed that once again it was not approved.

The Foundation, on behalf of members and all Australians in the greater community, put together a comprehensive submission to the PBAC demonstrating quality of life benefits for adults who receive growth hormone replacement. Our survey was quite comprehensive covering economic and mental health issues, the impact of deficiency on metabolism, relationships and clinical health.

To all you adults, young adults, parents and carers who wrote to members of Parliament, congratulations on an effort well done. The (now former) chair of the PBAC, Mr. Lloyd Sansom commented that the number of on-line consumer comments were over 100 which he congratulated us on. Recently he emphasised the influence of consumer impact statements (PharmaInFocus 5-11 Sept), saying they have been critical to the PBAC process and have changed a decision in four previous cases. SO, don't be discouraged – the fight is not over yet! Watch this space…..

The PBAC report of the Pfizer submission will be found on
http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-somatropin-july11
The most important line in the report is in the penultimate paragraph that 'A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine'.

APF has set out a simplified version of the report below, with some explanations of terms at the end:-

Product: Somatropin (Recombinant human growth hormone), injection
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application
The submission requested an extension of the current Section 100 (Human Growth Hormone Program) listing to include treatment of severe adult growth hormone deficiency (AGHD).

2. Background
Somatropin has been subsidised through PBS under the Section 100 Human Growth Hormone Program, in accordance with the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit' since August 1993.

- At the March 2008 meeting, the PBAC recommended amending the listing of Genotropin branded somatropin products to include improvement of body composition and short stature associated with Prader-Willi Syndrome (PWS) in patients up to 18 years of age on the basis of high but acceptable cost-effectiveness compared with placebo. Listing was effective 1 July 2009.
- In September 2010, new "Guidelines for the Pharmaceutical Benefits Scheme Growth Hormone Program" took effect which are an amalgamation of the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a

Pharmaceutical Benefit (July 2008)' and the 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit for the treatment of Prader-Willi Syndrome (February 2009)'.

3. Registration Status

Genotropin brand of somatropin is TGA registered for the following indications:

- Short stature due to decreased or failed secretion of pituitary growth hormone;
- **Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL;**
- Growth disturbances associated with gonadal dysgenesis (Turner's syndrome);
- Improvement of body composition and treatment of short stature associated with
  Prader-Willi syndrome (PWS) in paediatric patients;
- For treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73m^2.

4. Listing Requested and PBAC's View

The submission proposed to extend the current Section 100 (Human Growth Hormone Program) criteria for availability to read as follows:

> "Genotropin branded products are also available for the treatment of Prader-Willi Syndrome **and for the treatment of adults with severe growth hormone deficiency** in accordance with the 'Guidelines for the Pharmaceutical Benefits Scheme Growth Hormone Program".

5. Clinical Place for the Proposed Therapy

The submission proposed that the listing of Genotropin branded somatropin would provide a subsidised treatment option for severe AGHD patients with impaired quality of life.

6. Comparator

The submission nominated standard care (SC), which consists of regular monitoring by an endocrinologist, medical management of signs and symptoms and management of risk factors arising from AGHD as appropriate, as the main comparator.
The PBAC considered this appropriate.

7. Clinical Trials

The submission presented 39 randomised controlled trials comparing somatropin with placebo in patients with AGHD.

The PBAC noted that an impaired QoL at baseline (requested in the listing) was not an entry criterion for any of the trials, which limited the relevance of these trials to the requested listing.

As many publications and study reports were more than 10 years old, limited information was available on the trial methodology, and it was uncertain whether bias may have been introduced in the trials.

8. Results of Trials
Quality of life outcomes
The submission noted that none of the trials were restricted to patients with impaired QoL at baseline (requested indication).

The PBAC noted that the two trials that assessed QoL using the QoL-AGHDA (specific to the AGHDA patient population) did not present details about baseline values and improvement, but both reported no significant effect of treatment with somatropin.

9. Clinical Claim
The submission described somatropin as superior in terms of comparative effectiveness (improvement in QoL and body composition) and inferior in terms of comparative safety over placebo.

The PBAC considered the clinical benefit of somatropin was **uncertain**. The PBAC accepted the submission's claim that somatropin is inferior in terms of short-term safety to placebo. The PBAC considered that the long-term safety of somatropin is uncertain.

10. Economic Analysis
The submission estimated that the cost effectiveness ratio for somatropin was in the range of $45,000 - $75,000/QALY.

The PBAC considered that the cost effectiveness for somatropin compared to placebo treatment was likely to be higher than the specific figure arrived at in the submission because the submission may have:

- underestimated the cost:
- the daily dose of somatropin may have been underestimated;
- costs for the treatment of adverse events have been excluded; and
- costs of increased monitoring (thyroid function and glucose tolerance) were excluded;
- overestimated the QALY gain for somatropin:

11. Estimated PBS Usage and Financial Implications
The submission estimated the total net cost to the PBS to be less than $10 million year 5.

12. Recommendation and Reasons
The PBAC considered the comparator of standard care, consisting of regular monitoring by an endocrinologist, medical management of signs and symptoms, and management of risk factors arising from adult growth hormone deficiency (AGHD), appropriate.

The submission presented 39 randomised controlled trials comparing somatropin with placebo in patients with AGHD with a normal quality of life (QoL). The PBAC noted that an impaired QoL at baseline was not an entry criterion for the trials, which limited the relevance of these trials to the requested listing for patients with impaired QOL as measured by the QoL-AGDHA instrument.

- The PBAC accepted the submission's claim that somatropin is inferior in terms of short term safety to placebo. The PBAC considered that the long-term safety of somatropin is uncertain.
- The PBAC hence considered that the cost effectiveness ratios generated from the economic evaluation were highly uncertain.
- The PBAC hence rejected the submission on the basis of uncertain clinical benefit and uncertain and high cost effectiveness.
- The PBAC acknowledged and noted the consumer comments received in its consideration of somatropin.
- The PBAC recommended amending the wording of the listing of somatropin to correctly reflect the current version of the Guidelines for the PBS Growth Hormone Program, noting that there are no longer separate guidelines for the availability of growth hormone for the treatment of Prader-Willi Syndrome.
- The PBAC further recommended amending the wording of the listing of somatropin to remove the description of Genotropin branded products.

In lay-man terms -

- Bias may have been introduced in the trials

Bias in this case relates to whether the research has been influenced by factors other than the treatment. In particular, do these factors make the treatment look better than it really is.

- Baseline values

Baseline Quality of Life (QoL) values refers to the fact that the clinical trial patients did not have impaired QoL at the start of the trial (baseline), which is required for the PBS listing requested in the application. That is, the clinical trial data does not match up with the requested PBS listing. While there were lots of clinical trials in HGH, no trial was specifically conducted in patients with impaired Quality of Life

- Inferior in terms of comparative safety over placebo

Short term safety data is worse for the drug compared with no drug (placebo). All drugs have side effects. There is no adequate long term safety data comparing treatment with no drug.

- QALY

Quality adjusted life years (QALYs) are used to describe value for money. Patients with a medical condition can be allocated a life quality score (utility) from 1 (perfect health) to 0 (dead). This score is then multiplied by the time with the medical condition. For example 5 years with a life quality score of 0.9 = 4.5 QALYs.
Two treatments are compared using an incremental cost per QALY (difference in cost / difference in QALYs).
If the incremental cost/QALY is less than $45,000, then PBAC is more likely to approve the drug and if it is above $45,000 then PBAC is more likely to reject the drug.
The PBAC considered that the ICER for somatropin compared to placebo treatment was likely to be higher than the specific figure arrived at in the submission

- $10 million year 5

The PBAC submission requires a Budget impact analysis for the first 5 years of PBS listing.
If the cost of a new drug is greater than $10 million, then it needs to have Cabinet approval.