Annex II

Scientific conclusions and grounds for the amendment of the summaries of product characteristics and package leaflets presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of somatropin-containing medicinal products (see Annex I)

Somatropin is a recombinant human growth hormone (rhGH) acting on the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat.

Currently there are nine approved somatropin-medicinal products in the Union: Genotropin, Humatrope, Maxomat, Norditropin, Saizen, Zomacton approved via Mutual Recognition procedure (MRP) or Nationally (NAP) and Omnitrope, NutropinAq and Valtropin approved centrally (CAP).

Somatropin (rhGH) products have been available in Europe since the late 1980's for the treatment of several conditions associated with growth hormone deficiency and/or short stature.

In the Union, somatropin is approved to be used in children for growth hormone deficiency (including idiopathic growth hormone deficiency), growth failure in patients with Turner syndrome, chronic renal insufficiency or short stature homebox-containing gene (SHOX) deficiency, Prader-Willi syndrome and in patients born small for gestational age (SGA). Some indications are not approved for all somatropin containing medicines.

The safety of growth hormone therapy has been mainly based on large samples of patients followed in post-marketing databases during or not for long after treatment. Therefore, limited information on long-term safety of somatropin treatment is currently available.

Somatropin-treatment has been associated with tumour-promoting potential and this is currently reflected in the product information of all somatropin-containing medicinal products. Firstly due to the biological plausibility based on the established tumorigenic potential of insulin-like growth factor-1 (IGF-1), which is the key mediator of GH activity and secreted in response to GH receptor activation. Secondly, due to several published studies that reported a higher risk of tumour and/or tumour related mortality for patients treated with growth hormone (Swerdlow et al. 2002[1], Sklar et al. 2002[2] and by Ergun-Longmire et al. 2006[3]).

A large epidemiological study based on data from the Association France-Hypophyse registry was ongoing since 2007 – the French Santé Adulte GH Enfant (SAGHE) study. This long-term surveillance study collected data from all patients that were treated with rhGH in the period from 1985 to 1996 and who were older than 18 years of age at the time of data collection in 2007. The primary objective of the study was to evaluate the overall and cancer-related mortality and morbidity risks in comparison with risks in the general population.

All 10,330 patients were assigned to three risk categories for long-term mortality based on the clinical condition. The low risk population defined as treatment for idiopathic growth hormone deficiency, idiopathic short stature, short stature in children born short for gestational age, or isolated growth hormone deficiency was included in the mortality analysis (n=6,892 patients corresponding to 116,403 person-years of observation).

[1] Swerdlow AJ, Higgins CD, Adlard P, et al. Risk of cancer in patients treated with pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 2002; 360:273-277.

[2] Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: A report from the Childhood Cancer Survivor Study. J. Clin. Endocrinol. Metab. 2002;87:3136-3141

[3] Ergun Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W et al. Growth hormone treated and risk of second malignant neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 2006;91:3494-3498

On 9 December 2010, the French National Competent Authority (AFSSAPS) informed the European Commission, the European Medicines Agency and all Member States of unpublished results of the SAGHE study that showed an all-cause mortality significantly higher in children treated with rhGH (standard mortality ratio - SMR of 1.33, 95% CI 1.08;1.64). These results suggested an increased mortality with higher doses and due to diseases of the circulatory system (subarachnoid or intracerebral haemorrhage) and bone tumours.

This information was circulated in a rapid alert triggering a procedure under Article 107 of Directive 2001/83/EC, as amended. There were concerns on the impact of the results of this study on the benefit-risk balance of somatropin-containing medicinal products.

The CHMP reviewed all data submitted including data from the French SAGHE study and from clinical trials, registries, cohorts and safety databases (pharmacovigilance) as well as data available in the literature relating to the cardiovascular risk and risk of neoplasm associated with somatropin-treatment.

Results of the French SAGHE study, a long-term surveillance study in a high number of patients and with a mean follow up of 17 years suggested an overall increase of mortality in patients treated with somatropin for isolated growth hormone deficiency (GDH), idiopathic short stature (ISS) and short for gestational age (SGA) compared to the general population. Increased mortality was apparent when higher doses were used and due to subarachnoid or intracerebral haemorrhage and bone tumours.

However, this study presents significant methodological limitations that preclude these results to be regarded as robust. Namely, the general population used as reference group for the calculation of the standard mortality ratios leading to unmeasurable confounding. Also, the characteristics of the treated patients that p*er se* may be associated with increased mortality, even if in a low risk group (i.e. treated for isolated GHD, ISS and SGA).

Overall mortality risk was small, with an excess of 23 deaths over the 70 expected. Of the 93 all-cause mortality cases, 21 classified as resulting from "ill-defined conditions" are of unknown cause. The suggested increased risk with the higher doses is only statistically significant in the group treated with mean doses above 50 µg/kg/day (n=281). It is noted that in this group, 225 (80%) patients were part of a company-sponsored study conducted in children born short for gestational age (SGA) and overall this is considered a very small subpopulation for a clear association of the suggested risk with the dose. In addition the risk increased with short duration of treatment, nevertheless a sub-analysis by cumulative doses did not confirm this finding. Finally, data from the patient group that died due to diseases of the circulatory system showed that all but one had been treated for a diagnosis of growth hormone deficiency. No information on the presence of cardiovascular risk factors was available for 3 out of 9 patients. This information is very limited not allowing a conclusion with regards the cardiovascular risks. No data on the occurrence of non-fatal neoplasms in patients of the SAGHE study is, at the moment, available and the morbidity results are still is on-going.

All other data reviewed by the CHMP did not corroborate the results of the SAGHE study or did provide new or additional safety concerns.

Overall, in view of the limitations of the French SAGHE study the findings of an apparent increased risk of mortality in children treated with somatropin (increased risk with higher doses and relating to subarachnoid or intracerebral haemorrhage and bone tumours) cannot be regarded as robust data.

However, the results of the French SAGHE study are regarded as potential safety signal to be further considered in light of long term safety data that will become available in 2 years time, namely the results of the European SAGHE consortium study. The SAGHE study in Europe is part of the FP7 Health work programme and approximatelly the sample size is of 30,000 patients will be included in the 8 involved countries (France, Belgium, United Kingdom, Netherlands, Switzerland, Italy, Germany and Sweden). The study started on the 1st of June 2009 and results are expected to be available in 2013.

In view of all the above discussed, the Committee considered justified to harmonise or include , as appropriate, contraindications for all somatropin containing medicinal products with regards the potential for tumour-promoting associated with treatment. The specific wording to be include in section 4.3 of the SmPCs and reflected in the package leaflets of all somatropin-containing medicinal products was agreed (see Annex II).

This potential risk should also be reflected in the Risk Management Plan for all somatropin products as well as the potential risk of subarachnoid or intracerebral haemorrhage.

Finally, to address the potential signal of an increased risk with increased dose as suggested by the results of the French SAGHE study, it was agreed to emphasize in the product information of all somatropin-containing medicinal products that the maximum recommended daily dose should not be exceeded.

Grounds for amendment of the summaries of product characteristics and Package Leaflets

Whereas

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended for somatropin-containing medicinal products;

- The Committee considered the results of the French SAGHE study and all available data submitted from clinical trials, registries, cohorts and safety databases in relation to the cardiovascular risk and risk of neoplasm associated with somatropin-treatment.

- The Committee agreed that the French SAGHE study has significant methodological limitations (e.g. general population used as reference for the calculation of mortality). In view of these limitations, the Committee concluded that the study findings of an apparent increased risk of mortality in children treated with somatropin (increased risk with higher doses and relating to subarachnoid or intracerebral haemorrhage and bone tumours) cannot be regarded as robust.

- Other data reviewed did not corroborate the results of the SAGHE study, or provided additional safety concerns.

- The Committee agreed however, that the results of the French SAGHE study are regarded as potential safety signal. Considering previously published data and information already included in the Product Information for some somatropins, the Committee considered that it is justified to harmonise existing contraindications for all somatropin containing medicines when there is any evidence of activity of a tumour. This also needs to be reflected in the Risk Management Plans as well as the potential risk linked to subarachnoid or intracerebral haemorrhage. Furthermore, the Committee agreed to emphasise in the Product Information (section 4.4) the need for the maximum recommended dose not to be exceeded.

In view of the above, the CHMP has recommended the variation to the terms of the Marketing Authorisations for somatropin-containing medicinal products (see Annex I), for which the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III and subject to the conditions set out in Annex IV of this Opinion.