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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 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.

What is somatropin?

Somatropin is a copy of naturally occurring human growth hormone, produced by a method known as 'recombinant DNA technology'. Growth hormone promotes growth during childhood and adolescence, and also affects the way the body handles proteins, fats and carbohydrates.

Medicines containing somatropin are given by injection. They have been authorised in the EU since the 1980s through centralised or national procedures.[2] The approved indications vary for the different somatropin-containing medicines: they may be used as hormone replacement therapy, and to correct short stature (height) in children with certain genetic diseases (Turner syndrome or Prader Willi syndrome), children who have long-standing kidney problems and children born small for their gestational age.

Why was somatropin reviewed?

In December 2010, the French medicines regulatory agency was made aware of preliminary results of a long-term population-based study in France of patients treated during childhood with somatropin-containing medicines. The study, called 'Santé Adulte GH Enfant' (SAGhE) study, was initiated in October 2007 and aimed at improving knowledge on the safety and appropriateness of somatropin

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[2] The centrally authorised somatropin-containing medicines are NutropinAq, Omnitrope and Valtropin. The nationally authorised medicines are Genotropin, Humatrope, Maxomat, Norditropin, Saizen and Zomacton.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

treatment. It looked at data on 10,000 adults who started treatment between 1985 and 1996, using a mandatory national registry.

An analysis in approximately 7,000 of those patients who were treated for growth hormone deficiency and for gestational or idiopathic short stature showed a possible increased risk of mortality with somatropin compared with the general population. In particular, an increased risk of mortality due to bone tumours and cardiovascular events (such as bleeding in the brain) was seen. The risk appeared to be highest when doses higher than the ones approved were used.

Consequently, in December 2010 the French agency asked the CHMP to issue an opinion on the impact of these data on the benefit-risk balance of somatropin-containing medicines, and on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU. At the same time, the European Commission requested the CHMP to carry out the same assessment for the centrally authorised somatropin-containing medicines.

Which data has the CHMP reviewed?

The CHMP reviewed the available data on the safety of somatropin-containing medicines, including data from clinical trials, registries, and observational studies, as well as reports of side effects from post-marketing surveillance. The CHMP also looked into additional data from the unpublished French SAGhE study.

What are the conclusions of the CHMP?

The CHMP concluded that the French SAGhE study had significant methodological limitations and that the results could not be considered robust. After assessing all other available safety data on somatropin, the CHMP concluded that the potential signal of an increased risk of mortality seen in the French study is not corroborated by any other data, and that the benefit-risk balance of somatropin-containing medicines has not changed.

However, the Committee noted that the available data on the long-term effects of somatropin treatment are very limited. Further mortality data from the European SAGhE study will be available by the end of 2012, and the CHMP considered an analysis of these results to be essential to address any concerns raised by the French study.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefit-risk balance of somatropin-containing medicines remains positive when used in the approved indications at the approved doses. However, to ensure that somatropin-containing medicines are used appropriately, the CHMP recommended that specific wording be included in the product information of all somatropin-containing medicines. In particular, the harmonised wording will emphasise that somatropin must not be used if there is any evidence of tumour activity, and that the maximum recommended daily dose should not be exceeded.

What are the recommendations for patients and healthcare professionals?

- Patients and healthcare professionals are reminded that the benefits of somatropin continue to outweigh its risks in the approved indications.
- Somatropin must not be used in patients with any evidence of tumour activity.
- The maximum recommended daily dose should not be exceeded.
- Patients or their carers who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on 27 February 2012.