HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 July 2008

UMATROPE 6 mg/3 ml powder and solvent for solution for injection in a multiple dose cartridge
Pack of 1 cartridge and 1 syringe prefilled with solvent (CIP: 342 158-7)

UMATROPE 12 mg/3 ml powder and solvent for solution for injection in a multiple dose cartridge
Pack of 1 cartridge and 1 syringe prefilled with solvent (CIP: 342 159-3)

UMATROPE 24 mg/3 ml powder and solvent for solution for injection in a multiple dose cartridge
Pack of 1 cartridge and 1 syringe prefilled with solvent (CIP: 342 160-1)

Applicant: LILLY FRANCE

somatropin

ATC code: H01AC01

List I
The initial annual hospital prescription is reserved for specialists in paediatrics and/or in endocrinology and metabolic diseases working in specialist departments of paediatrics and/or endocrinology and metabolic diseases.

Date of marketing authorisation:
Initial marketing authorisation: 21 November 1995
Extension of indication to patients who have growth failure associated with SHOX deficiency: 15 February 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication to patients who have growth failure associated with SHOX deficiency.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

somatropin

1.2. Background

The first proprietary product indicated for the treatment of patients who have growth failure associated with SHOX deficiency.

1.3. Indication

"Paediatric patients:
Long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

Treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis.

Treatment of growth retardation in prepubertal children with chronic renal insufficiency.

Treatment of patients who have growth failure associated with SHOX (Short stature HomeobOX-containing gene) deficiency, as confirmed by DNA analysis.

Umatrope is also indicated for growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (height velocity SDS < 0 during the last year) by 4 years of age or later.

Adult patients:
Umatrope is indicated for replacement therapy in adults with pronounced growth hormone deficiency.
Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth deficiency.
In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations (<-2 SDS), who may be considered for one test. The cut-off point of the dynamic test should be strict."

1.4. Dosage

"UMATROPE in cartridges is administered by subcutaneous injection after reconstitution.
The dosage and administration schedule should be personalised for each individual.

Paediatric patients with SHOX deficiency:
The recommended dosage is 0.045-0.050 mg/kg of body weight per day given as subcutaneous injection.
The subcutaneous injection sites should be varied in order to avoid lipo-atrophy."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

H : Systematic hormonal preparations, excluding sex
H01 : Pituitary and hypothalamic hormones and analogues
H01A : Anterior pituitary lobe hormones and analogues
H01AC : Somatotropin and analogues
H01AC01: : Somatropin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

No other proprietary product has an indication for the treatment of patients who have growth failure associated with SHOX (Short stature HomeobOX-containing gene) deficiency, as confirmed by DNA analysis.
All growth hormones are included on the list of medicines reimbursed by National Insurance for the indication “Growth disturbance associated with Turner syndrome”. Short stature in Turner syndrome appears to be associated with a SHOX gene disorder (see Orphanet). Growth hormone indications are summarised in Table 1.

Table 1: summary of growth hormone indications

	Growth retardation in paediatric patients							**Adults**
	associated with growth hormone deficiency	associated with Turner syndrome	associated with renal insufficiency in prepubertal children	associated with renal insufficiency in pubertal children	Associated with Prader-Willi syndrome	Growth retardation in children born small for their gestational age	Intrauterine growth retardation	Growth hormone deficiency
Génotonorm®	yes	yes	yes	yes	yes	yes	no	yes
Maxomat®	yes	yes	no	no	no	no	yes	no
Norditropine®	yes	yes	yes	no	no	yes	no	yes
Nutropinaq®	yes	yes	yes	no	no	no	no	yes
Saizen®	yes	yes	yes	no	no	yes	no	yes
Umatrope®	yes	yes	yes	no	no	yes	no	yes
Omnitrope®	yes	yes	yes	yes	yes	yes	no	yes
Zomacton®	yes	yes	no	no	no	no	no	no

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The company submitted the results of a randomised, open-label clinical study – GDFN – comparing UMATROPE (n=27) and absence of treatment (n=25) in 52 patients with a SHOX gene disorder. A 3rd group was also formed of patients with Turner syndrome (n=26)[1].
For inclusion in the study, patients with SHOX gene disorder had to have a bone age of less than 10 years for boys and less than 8 years for girls. Patients with Langer syndrome were excluded.
UMATROPE treatment was administered at a dosage of 0.05 mg/kg/day for 1 year, with the opportunity to continue the allocated treatment for one additional year (extension period A).
A second extension period (extension period B) was specified in the protocol, during which all patients were treated with UMATROPE either until they achieved their final height or until October 2010. The company did not submit results of patient follow-up during this second extension phase to the Transparency Committee.

Primary endpoint: first-year height velocity (HV), as a standard deviation score
HV SDS = (patient's HV – mean HV for age and gender) / standard deviation
where HV (cm/yr) = height after 1 year – height at baseline
A difference in height velocity between the treated-SHOX and untreated-SHOX groups was considered clinically significant if it exceeded 2 cm/yr. No details are given in the publication of how the required number of subjects was calculated. These results were analysed on an intention-to-treat basis.

Secondary endpoints:
Second-year height velocity
Height
First-year height variation
Safety after 2 years

These results were analysed on a per-protocol basis.

[1] Blum et al., J Clin Endocrinol Metab 92: 219-228, 2007

3.1. Efficacy

The results are shown in tables 2 and 3, below.

Table 2: First-year height velocity (HV) in patients with SHOX gene disorder:

	UMATROPE	Untreated	p
HV (cm/yr)	8.68 ± 1.56	5.15 ± 1.13	<0.001
HV SDS (SDS)	+2.96	-0.73	<0.001

Table 3: Second-year height velocity in patients with SHOX gene disorder:

	UMATROPE	Untreated	p
HV (cm/yr)	7.33 ±1.06	5.37 ± 1.23	<0.001
HV SDS (SDS)	+2.31	-0.44	<0.001

After 2 years' treatment, 41% (n=11) of treated SHOX patients and 4% (n=1) of untreated SHOX patients had achieved normal height for their age and gender (> -2 SD).

The results for the treated Turner syndrome patients are as follows: First year HV (cm/yr): 8.9 ± 0.4, and second year HV (cm/yr): 7,0 ± 0.2. The study design means that only a descriptive comparison can be made with the patients who have SHOX gene disorder.

The Transparency Committee regrets that no data were supplied on the final height of the children with SHOX gene disorder who were included in this study.

The company also analysed the final height of patients from 3 different sources:

- the GDFN study
- the GeNeSIS study: an observational study following UMATROPE-treated patients to adulthood
- a survey of doctors with experience of giving UMATROPE therapy to small children with SHOX gene disorder.

All these patients had an initial height SDS of < -1.5, genetically confirmed SHOX gene disorder (n=14) or Turner syndrome (n=158), and had been treated for over 2 years with growth hormone (UMATROPE, GENOTONORM or SAIZEN) at an initial dose of 0.25 ± 0.11 mg/kg/week (lower than recommended in the marketing authorisation). The generally accepted definition of short stature is height < -2 SD. The results will not be given because of the design limitations of this study.

3.2. Adverse events

One patient in the untreated SHOX group was lost to follow-up.
No severe adverse events were reported with UMATROPE, and no adverse event resulted in premature discontinuation of treatment in the two years of monitoring.
The tolerance profile of UMATROPE in patients with SHOX gene disorder was the same as in patients treated for other indications (see the SPC). In the current state of knowledge, however, little is known about the potential effect in adulthood of treatment administered during childhood or adolescence.

3.3. Conclusion

The company submitted the results of a randomised, open-label clinical study – GDFN – comparing UMATROPE (n=27) and absence of treatment (n=25) in 52 patients with a SHOX gene disorder. A 3rd group was also formed of 26 patients with Turner syndrome[2].

[2] Blum et al. J Clin Endocrinol Metab 2007;92: 219-228.

In the patients with SHOX gene disorder who were treated with UMATROPE, first and second-year height velocity was greater than in the untreated patients.
The study design means that only a descriptive comparison can be made between the Turner syndrome patients and the patients with SHOX gene disorder.
The Transparency Committee regrets that no data were supplied on the final height of the children with SHOX gene disorder who were included in this study.

The safety profile of UMATROPE in patients with SHOX gene disorder was the same as in patients treated for other indications. In the current state of knowledge, however, little is known about the potential effect in adulthood of treatment administered during childhood or adolescence; this is a matter of concern.

There is a limited amount of data. The trial design was not ideal for evaluating the objective benefit in terms of stature progression in children who have growth failure associated with SHOX deficiency.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

This condition is characterised by the development of disability and/or a marked deterioration in the quality of life.
These proprietary products are intended for symptomatic treatment.
The efficacy/adverse effects ratio of these products in this indication is moderate.
These products are for use as first-line treatment.
There are no alternative treatments to these medicinal products.
Public health benefit:

Growth failure associated with SHOX deficiency has variable clinical consequences and may lead to a impairment of quality of life and a psychosocial impact. This condition results in a low public health burden because of its rarity.
In light of the available data, and since:
- the effect of UMATROPE on the final height of patients treated under this extension of indication has not been sufficiently demonstrated, and
- data are lacking on the improvement in treated children's quality of life and on the morbidity resulting from the pathological conditions associated with SHOX deficiency, the public health impact of UMATROPE cannot be evaluated.

There is no certainty that the experimental data can be transposed into real life, particularly since patient compliance with treatment involving daily subcutaneous injections for several years cannot be guaranteed.
There is expected to be an impact on the provision of healthcare and the health service given the need to perform diagnostic genetic testing for SHOX deficiency. Eligibility criteria for the test must be defined and the diagnostic power of the test must be determined so that patients likely to benefit from UMATROPE in this extension of indication may be effectively identified.
Consequently, UMATROPE is not expected to benefit public health in this extension of indication.

The actual benefit of these medicinal products is moderate.

4.2. Improvement in actual benefit

Improvement in actual benefit (IAB) level IV in the management of short stature of children who have a SHOX gene disorder as confirmed by DNA analysis.

4.3. Therapeutic use

UMATROPE is the first proprietary product indicated for the treatment of patients who have growth failure associated with SHOX (Short stature HomeobOX-containing gene) deficiency, as confirmed by DNA analysis.
It should be noted that all growth hormone-based products are indicated for patients with growth failure associated with Turner syndrome and that short stature in Turner syndrome is likely to be associated with complete or partial loss of the SHOX gene.

4.4. Target population

Approximately 2% of children are considered to be of short stature[3,4]. In 80% of cases this short stature is idiopathic, and 2.2% of these patients have a SHOX gene disorder[4]. If these data are applied to the population of prepubertal children aged 2 years and above in France[5], the number of children with a SHOX gene mutation will be in the order of 3,000.
Experts believe this is probably the maximum number.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indications and at the dosage stated in the marketing authorisation. As indicated in the SPC, a molecular diagnosis of SHOX deficiency is required before these products can be prescribed.

For children, in the indication "treatment of patients who have growth failure associated with SHOX (Short stature HomeobOX-containing gene) deficiency, as confirmed by DNA analysis", the Transparency Committee will make future confirmation of its favourable opinion to the implementation of a follow-up study and the results thereof. The aim of such a study will be to describe the following aspects in real-life treatment situations:
- the characteristics of the patients receiving the treatment (age, height, pathological condition associated with the SHOX gene disorder, diagnostic genetic testing method used, etc.)
- compliance, duration of treatment and reasons for discontinuing treatment
- effect on growth, the children's final height, morbidity connected to the pathological conditions associated with the deficiency
- occurrence of adverse effects.
The duration of the study must be justified by an independent scientific committee.

4.5.1. Packaging: Appropriate to prescription requirements.

4.5.2. Reimbursement rate for this extension of indication: 100%

4.5.3. Exception drug status:

The Transparency Committee wishes these proprietary products to have exception drug status for this indication.

[3] Arch Physiol Biochem. 2007 Jun; 113**(3)**:116-23
[4] J Med Genet. 2007 May; 44**(5)**:306-13.
[5] INED 2008: 9,439,000 boys aged 2-14 years and girls aged 2-12 years.