HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 December 2007

INCRELEX 10 mg/ml, solution for injection
Box of 1 x 4 ml vial (CIP code: 381 467-7)

BEAUFOUR IPSEN PHARMA

Mecasermin

List I
Medicinal product reserved for hospital prescription by specialists in paediatrics or in endocrinology and metabolic diseases.
Medicinal product requiring specific monitoring during treatment.
Orphan drug

Date of Marketing Authorisation: 13 August 2007
Centralised European marketing authorisation granted under exceptional circumstances (the SPC states that the EMEA will review any new information which may become available once a year and the SPC will be updated as necessary).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use in hospitals.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
Mecasermin

1.2. Background
First recombinant IGF-1.
Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1 (IGF-1) produced in *Escherichia coli*.

1.3. Indication
"For the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD).

Severe primary IGFD is defined by:
• height standard deviation score ≤ -3.0 and
• basal IGF-1 levels below the 2.5th percentile for age and gender and
• GH sufficiency.
• Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test."

1.4. Dosage
Treatment with INCRELEX should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.

The dose should be individualised for each patient. The recommended starting dose of mecasermin is 0.04 mg/kg twice daily by subcutaneous injection. If no significant treatment-related adverse events occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with severe primary IGFD.

If the recommended dose is not tolerated by the subject, treatment with a lower dose can be considered. Treatment success should be evaluated based on height velocities. The lowest dose that was associated with substantial growth increases on an individual basis was 0.04 mg/kg BID.

INCRELEX should be administered shortly before or after a meal or snack. If hypoglycaemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat, for any reason, INCRELEX should be withheld. The dose of mecasermin should never be increased to make up for one or more omitted doses.

Injection sites should be rotated to a different site with each injection.

INCRELEX should be administered using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

INCRELEX is not recommended for use in children below age 2 due to a lack of data on safety and efficacy.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification 2007

H	Systemic hormonal preparations, excl. sex hormones and insulins
H01	Pituitary and hypothalamic hormones and analogues
H01A	Anterior pituitary lobe hormones and analogues
H01AC	Somatropin and somatropin agonists
H01AC03	Mecasermin

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

No other medicinal product is indicated in the management of severe primary IGF-1 deficiency (primary IGFD).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The marketing authorisation for INCRELEX is based on the results of five clinical studies to evaluate the efficacy and safety of INCRELEX in children and adolescents with growth failure due to severe primary IGF-1 deficiency (primary IGFD).

Three initial studies were conducted: a phase II open-label study (F0206s, n=8), a phase III open-label study (F0632g, n=6) and a phase III crossover, double-blind, placebo-controlled study (F0375g, n=8).

One phase III open-label study (F0671g) included 21 subjects from the previous studies and 2 new patients.

A follow-up study (study 1419, n=76), currently in progress, has included the 23 patients from study F0671g plus 53 new subjects. Only interim results from this study are available.

The inclusion criteria were as follows: age above 18 months, extremely short stature (below -2 SD for their age), slow growth rate (less than the 50^{th} percentile for their age for more than 6 months), low serum IGF-1 concentrations (below -2 SD for their age), and normal growth hormone level.

In these studies, patients were given subcutaneous doses ranging from 60 to 120 µg/kg twice daily (BID).

RESULTS:

Baseline patient characteristics were as follows:
- chronological age: 6.8 ± 3.8 years
- bone age (years): 3.9 ± 2.8 years
- height: 85.0 ± 15.3 cm; -6.7 ± 1.8 SDS (standard deviation score)
- height velocity: 2.8 ± 1.8 cm/yr (-3.3 ± 1.7 SDS)
- serum IGF-1 level: 21.9 ± 24.8 ng/ml (-4.4 ± 2.0 SDS)

In study 1419, 62 patients had at least one year of treatment. Of these 62 patients, 38 (61%) were male; 49 (79%) were Caucasian; and 56 (90%) were prepubertal. Fifty-three patients (85%) had Laron syndrome, 7 (11%) had GH gene deletion, 1 (2%) had neutralising antibodies to GH, and 1 (2%) had an isolated GH gene deficiency (type 1A).

3.1.1. Studies F0375g, F0206s, F0632g and F0671g

Methodological details and the main results for these four studies are given in Table 1 below.

In the double-blind, crossover study F0375g, only 4 of the 8 patients included completed the two 6-month periods of treatment. The increase in height velocity in these two periods was: +7.1 cm/yr, +3.7 cm/yr and +3.2 cm/yr compared with baseline in three patients treated with INCRELEX and +5.6 cm/yr in the one patient on placebo.

In the three open-label studies, an annual improvement in height velocity was observed. It is difficult to evaluate the relevance of this result given the open-label nature of the study and the low number of patients included. In addition, the size of the effect observed was not uniform from one study to another.

Table 1: Summary of studies F0375g, F0206s, F0632g and F671g

Study	Experimental design	Duration of treatment (months)	Patients Population Phenotype	Treatments	Primary endpoint	Results
Study versus placebo						
F0375g	phase III, randomised, double-blind, crossover, placebo-controlled	2 x 6 months 3 month wash-out	N = 8 Laron (7), GH gene deletion (1)	INCRELEX - 80 µg/kg BID for 3 days, then 120 µg/kg BID Days 4 and 5, then - randomisation on Day 6 to INCRELEX or placebo	Annual height velocity (improvement over baseline)	Results available for 4 of the 8 patients. Height velocity: Increlex then placebo group: - one patient: 9.8 cm/yr (+7.1 cm/yr) on Increlex then 2.2 cm/yr on placebo - one patient: 7.7 cm/yr on Increlex then 2.9 cm/yr on placebo Placebo then Increlex group: - one patient: 0.8 cm/yr on placebo then 7.2 cm/yr (+3.2 cm/yr) on Increlex - one patient: **7.6 cm/yr (+5.6 cm/yr) on placebo** then maintained at 7.7 cm/yr after Increlex.
Non-comparative studies						
F0206s	Phase II, open-label, single centre study	2 years	N = 8 Laron (5), Acquired GH resistance (3)	INCRELEX: - 40 µg/kg BID, then 20 µg/kg increase every other day up to 120 µg/kg BID	Annual height velocity (improvement over baseline)	At 1 year: 9.3 cm/yr (annual increase of 5.4 cm/yr) At 2 years: 6.2 cm/yr (annual increase of 2.3 cm/yr)
F0632g	Phase III, open-label, multicentre study	1 year	N = 6 Laron (2), GH gene deletion (3) Unknown (1)	INCRELEX - 60 µg/kg BID	Annual height velocity (improvement over baseline)	At 1 year: 5.4 cm/yr (annual increase of 4.2 cm/yr)
F0671g	Phase III, open-label, multicentre study	2 years	N = 23 Laron (16), GH gene deletion (7)	INCRELEX - 80 µg/kg BID (n=1) then - 100 µg/kg BID (n=3), then - 120 µg/kg BID (n=19)	Annual height increase after 1 year and 2 years of treatment compared with baseline height in cm	At 1 year: + 6.1 cm (± 3.34) At 2 years: + 10.8 cm (± 2.8)

3.1.2. Open-label follow-up study: study 1419[1]

This study included 76 patients (23 from the 4 previous studies and 53 new subjects). Only 62 patients have had the treatment for at least one year. Interim results observed after 8 years of treatment are only available for 14 patients (see Table 2).

In subjects who received doses of 100-120 µg/kg BID, the mean height velocity was 8 cm/yr after the first year of treatment and 5 cm/yr in years 2 to 8.

Height in adulthood is only known for 6 patients: 164.4 cm, 150.2 cm, 112 cm, 142 cm, 121.2 cm and 120.8 cm.

Table 2: Annual height results for each year of INCRELEX treatment

	Baseline	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**
Height velocity (cm/yr)									
n	59	59	54	48	39	21	20	16	14
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.4)	5.5 (1.9)	4.7 (1.4)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.5 (1.2)
Mean (SD) of the difference from baseline		+5.2 (2.6)	+3.0 (2.3)	+2.6 (2.3)	+1.6 (2.1)	+1.5 (1.8)	+1.5 (1.7)	+1.0 (2.1)	+0.9 (2.4)
p-value for the difference from baseline		<0.0001	<0.0001	<0.0001	<0.0001	0.0015	0.0009	0.0897	0.2135
Height velocity SDS									
n	59	59	53	47	38	19	18	15	12
Mean (SD)	-3.3 (1.7)	1.9 (2.9)	-0.2 (1.6)	-0.3 (2.0)	-0.7 (1.9)	-0.6 (2.1)	-0.4 (1.4)	-0.4 (1.9)	-0.3 (1.8)
Mean (SD) of the difference from baseline		+5.1 (3.1)	+3.2 (2.2)	+3.1 (2.4)	+2.5 (2.1)	+2.5 (2.2)	+2.7 (1.7)	+2.5 (2.1)	+2.8 (2.7)
p-value for the difference from baseline [1]		<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0003	0.0041
Height SDS									
n	62	62	57	51	41	22	20	16	14
Mean (SD)	-6.7 (1.8)	-5.9 (1.7)	-5.6 (1.8)	-5.3 (1.8)	-5.3 (1.8)	-5.5 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (1.9)
Mean (SD) of the difference from baseline		+0.8 (0.5)	+1.1 (0.8)	+1.4 (1.0)	+1.4 (1.1)	+1.4 (1.3)	+1.4 (1.2)	+1.4 (1.1)	+1.6 (1.1)
p-value for the difference from baseline [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001

SD = standard deviation; SDS = standard deviation score

[1] p-values for comparison versus baseline were *calculated using paired* t*-test method.*

[1] Chernausek *et al.* Long-term treatment with recombinant Insulin-like Growth Factor (IGF-1) in children with severe IGF-1 deficiency due to growth hormone insensitivity, The Journal of Endocrinology & Metabolism, July 2007,92:902-10.

3.2. Adverse effects

In these studies, 51 of the 76 patients (67%) experienced adverse effects considered to be linked to the treatment.

The most commonly observed adverse events were as follows:

- hypoglycaemia (47%, n=36) giving rise to seizure in 5% of cases
- lipohypertrophy at the injection site (32%, n=24)
- tonsillar hypertrophy (16%, n=12)
- ear and hearing disorders: otitis (16%, n=12), hypoacusis (20%, n=15)
- respiratory disorders: snoring (22%), sleep apnoea syndrome (4%)
- intracranial hypertension (4%, n=3)
- lymphoid hypertrophy requiring surgery in 11% of cases (n=8).

3.3. Conclusion

The efficacy and safety data for INCRELEX in the treatment of growth failure in children and adolescents with primary IGFD are derived from one double-blind study (F0375g), three open-label studies (F0206s, F0671g and F0632g) and one follow-up study (1419).

The results of these studies show an improvement in annual height velocity. It is difficult to evaluate the relevance of these results given the open-label nature of three of the studies, the low number of patients included, and the lack of uniformity in the size of the effect from one study to another.

The open-label follow-up study involving 76 patients (treated with doses of 100-120 µg/kg BID), most of whom had been included in the previous studies, reveals a mean height velocity of 8 cm/yr after the first year of treatment and 5 cm/yr in years 2 to 8. This study is still in progress. Interim results observed after 8 years of treatment are only available for 14 patients. The impact of INCRELEX on height in adulthood is only known for 6 patients.

In these studies, the patients had a slower height velocity (velocity -3.3 ± 1.7 SDS) and a more severe mean growth failure prior to treatment (height -6.7 ± 1.8 SDS) than that specified in the indications in the marketing authorisation (height ≤ -3 SD).

The main adverse events are hypoglycaemia (47%), lipohypertrophy at the injection site (32%), tonisllar hypertrophy (16%) and ear and hearing disorders. In the absence of firm data on the potential development of anti-IGF-1 antibodies, there remains some uncertainty as to whether efficacy is maintained in the longer term.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Severe IGF-1 deficiency growth failure is a rare and serious disease, which progresses towards disability and a marked deterioration in quality of life.

This medicinal product is used for replacement therapy.

This medicinal product is a first-line medicine.

There is no alternative medication.

The efficacy/safety ratio for this medicinal product is high.

Public health benefit:
Severe IGF-1 deficiency growth failure is a serious clinical condition that affects quality of life and has a psychosocial impact. The public health burden that it causes, however, is low because of its rarity.
Since the emergence of orphan drugs is considered an identified priority (GTNDO, Rare Disease Plan), the treatment of this condition is a public health need.
In light of the available data and particularly since the effect of INCRELEX on definitive height has not been demonstrated sufficiently well and there are no data on these patients' quality of life, the impact that this medicinal product is expected to have on morbidity and quality of life compared with usual management cannot be quantified.
In addition, because of uncertainty regarding long-term safety of and compliance with this INCRELEX treatment, there is no guarantee that the results of the trials can be transposed into clinical practice (8-year follow-up data are only available for 14 patients).
Consequently, on the assumption in the current state of knowledge that INCRELEX may provide a partial response to the identified public health need, this product is expected to be of public health benefit. This benefit can only be low at best.
** National Technical Group for Defining Public Health Objectives (DGS-2003)*

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

INCRELEX provides a moderate improvement in actual benefit (IAB level III) in the management of children and adolescents (2-16 years of age) with growth failure due to severe primary IGF-1 deficiency (primary IGFD).

4.3. Therapeutic use[2][3]

Growth failure with severe primary IGF-1 deficiency (primary IGFD) is characterised by IGF-1 deficiency combined with normal endogenous GH production. Patients are characterised by a reduced height velocity from childhood, lack of a growth spurt at puberty and severe dwarfism in adulthood.

[2] Orphanet – September 2002.
[3] Woods KA, Dastot F, Preece MA, Clark AJ, Postel-Vinay MC, Chatelain PG, *et al.* Phenotype: genotype relationships in growth hormone insensitivity syndrome. J Clin Endocrinol Metab 1997;82(11):3529-35.

Severe primary IGF-1 deficiency covers several genetic anomalies that have not all been documented. The extent and presence of each symptom and clinical characteristic vary from one individual to another, and it is difficult to make a link between patients' phenotypes and their genotypes.

One form of this deficiency is Laron syndrome, a recessive autosomal disease characterised by severe dwarfism, growth hormone (GH) receptor dysfunction, an inability to produce IGF-1 in response to GH, and normal or raised levels of GH.
Laron syndrome is the result of a mutation of the GHR gene on chromosome 5.

These patients are not GH deficient, and they are not expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting a standardised test for the generation of IGF-1 by GH; molecular analysis of GHR and GH1 gene anomalies is also recommended before treating a patient with INCRELEX.

No treatment is currently available. INCRELEX is therefore the first recombinant replacement medicine available for the management of these children and adolescents (2-16 years of age).

4.4. Target population[4]

The target population for INCRELEX comprises children and adolescents (2-16 years of age) with growth failure due to severe primary IGF-1 deficiency (primary IGFD), as defined by

- height ≤ -3 SDS
- plasma IGF-1 level below the 2.5th percentile (< -2 SD) for their age and gender
- normal GH level (non-deficient response in a GH secretion test)
- exclusion of secondary forms of IGF-1 deficiency, such as for example malnutrition, hypothyroidism, or chronic treatment with anti-inflammatory doses of glucocorticoids.

According to INSEE data, the population of children and adolescents aged between 2 and 16 is approximately 11 million.

Of these patients, 3% met the criterion of small stature, i.e. roughly 330 000 patients.[4]

Since the available epidemiological data are very limited, the target population for INCRELEX can only be estimated with a large degree of uncertainty. Nevertheless, based on the rare data that are available and on expert opinion, the target population for INCRELEX may be estimated to be in the order of 250-300 patients.

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 indication in the marketing authorisation.

4.5.1. Exception drug status:
The Transparency Committee wishes this medicinal product to have exception drug status.

4.5.2. Prescription requirements:
The diagnosis of the diseases involved, the prescribing of INCRELEX and the monitoring of the patients should all be conducted under the authority of the National Reference Centre and/or the centres of expertise for rare growth disorders.

4.5.3. Follow-up:

[4] Bryant *et al.* Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. Health technology assessment, NHS R&D HTA Programme 2002.

Study objectives:
The Transparency Committee would like to see a long-term monitoring study set up involving all patients treated with INCRELEX in France (an exhaustive registry), in order to document the following points under actual treatment conditions:

- The characteristics of the patients receiving this treatment, including biological aspects, in order to ensure that they have been correctly identified as being covered by this indication (patients with growth failure and severe primary IGF-1 deficiency).
- Changes in INCRELEX dosage (doses and duration of treatment)
- Changes in IGF-1 levels during treatment
- Compliance and the reasons for discontinuing treatment
- The impact of INCRELEX treatment on the children's growth and definitive height and their bone age
- The impact of INCRELEX treatment on their quality of life.

The duration of the study should be approved by an independent scientific committee.
If scheduled or ongoing studies, in particular within the scope of the European Risk Management Plan, cannot answer all the questions raised by the Transparency Committee, a specific study should be conducted.

Finally, the Committee points out that it will re-evaluate this medicinal product annually in light of the new data that becomes available.

4.5.4. Packaging: Appropriate to prescription requirements.

4.5.5. Reimbursement rate: 100%