increlex®
mecasermin

Physician information about Increlex®

This is an information document as described in the Physician's Prescribing Information of Increlex. A link to current prescribing information can be found on the back cover.

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important risks and it is advised therefore that it be read carefully before prescribing/dispensing/administering the product.

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Increlex® - The therapy for severe primary IGF-1 deficiency

- **Increlex® is recombinant human insulin-like growth factor-1 (rhIGF-1), which has a molecular structure identical to that of endogenous human IGF-1.**
- **A diagnosis of severe primary IGF-1 deficiency includes patients with low IGF-1 levels due to insensitivity to Growth Hormone (GH) associated with mutations in the GH receptors, in the post-GHR signalling pathway and defects in the IGF-1 gene. SPIGFD patients are not GH deficient, and they cannot, therefore, be expected to respond adequately to exogenous GH treatment.**
- **Increlex® is indicated for the long-term treatment of children and adolescents from 2 to 18 years with growth problems due to confirmed severe primary IGF-1 deficiency.**

Severe primary IGF-1 deficiency is defined by:

- **Height standard deviation scores ≤ -3.0 and**
- **Basal IGF-1 levels below the 2.5th percentile for age and gender and**
- **Growth hormone (GH) sufficiency**
- **Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids**

Administration

- Increlex® is a solution for injection, provided in vials of 40 mg of mecasermin (10 mg/ml).
- The recommended initial dose is 0.04 mg/kg twice daily by subcutaneous injection. If well tolerated for at least a week, the dose can be increased by 0.04 mg/kg per dose up to the maximum of 0.12 mg/kg twice daily and should not be exceeded as this may increase the risk of benign and malignant neoplasia. Prescribers should refer to the Increlex dose guide for further information on calculating the correct dose for each patient according to their weight.
- The site of injection site must be rigorously rotated at each administration to avoid lipohypertrophy at the injection site.
- Increlex® must always be administered shortly before or just after meals to avoid hypoglycaemic episodes (which can occur in the initial phase of treatment, decreasing with continuation of treatment)[1]. Symptomatic hypoglycaemia has generally been shown to be avoided when a meal or snack is consumed either shortly before or after the administration of Increlex.
- Patients and their parents/caregivers should be instructed on how to recognise the symptoms and signs of hypoglycaemia and how to prevent it.[2] They should also receive instruction on the treatment of severe hypoglycaemia should it occur (e.g., injection of glucagon).
- If the patient is unable to eat, for any reason, Increlex should be withheld. The dose of Increlex should never be increased to make up for one or more omitted doses.

Safety

Benign and Malignant Neoplasms[3]

Due to the increased risk of benign and malignant neoplasms with Increlex® use, it is contraindicated in patients with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia.

There have been post-marketing reports of benign and malignant neoplasms in children and adolescents who have received treatment with INCRELEX. These cases represented a variety of different malignancies and included rare malignancies usually not seen in children. The risk of developing neoplasms may be higher in patients who are not receiving Increlex® as indicated or receiving it at higher than recommended dosage. Current knowledge of IGF-1 biology suggests that IGF-1 plays a role in malignancies in all organs and tissues. Physicians should therefore be vigilant of any symptoms of potential malignancy.

In addition, parents should be educated on signs and symptoms of neoplasms. This would increase the likelihood of any neoplasm development being recognised and appropriate medical care sought as early as possible.

Hypoglycaemic effects

Increlex® should be administered shortly before or after a meal or snack, because it may have insulin- like hypoglycaemic effects. Special attention should be paid to young children, children with a history of hypoglycaemia and children with inconsistent food intake. Patients/caregivers should avoid engaging in any high-risk activities within 2-3 hours after dosing, particularly at the initiation of INCRELEX treatment, until a well-tolerated dose of Increlex® has been established3. If a person with severe hypoglycemia is unconscious or otherwise unable to ingest food normally, an injection of glucagon may be required. Persons with a history of severe hypoglycemia should have glucagon available. At the time of initial prescription, physicians should educate parents on the signs, symptoms and treatment of hypoglycaemia, including injection of glucagon.

Doses of insulin and/or other hypoglycaemic agents may need to be reduced for diabetic patients using Increlex®.

- **Cardiovascular anomalies**

  Echocardiogram is recommended before initiation of INCRELEX treatment in all patients. Patients who terminate treatment should also have an echocardiogram. Patients with abnormal echocardiogram findings or cardiovascular symptoms should be followed regularly with echocardiogram procedures.

- **Lymphoid hypertrophy**

  Due to the possibility of hypertrophy of the lymphoid tissue (e.g., tonsillar), the patient's ears, nose and throat should be examined periodically to rule out potential complications or to initiate appropriate treatment, in the event of clinical symptoms (e.g., snoring, chronic exudate from the middle ear).[3]

- **Intracranial hypertension**

  Due to the possibility of intracranial hypertension (IH), a routine fundoscopic examination should be performed prior to beginning treatment, periodically during the course of the treatment and if clinical symptoms occur (e.g., vision problems, severe persistent headache, nausea and/or vomiting).[3]

- **Slipped capital femoral epiphysis and progression of scoliosis**

  Slipped capital femoral epiphysis (with the potential to lead to avascular necrosis) and progression of scoliosis can occur in patients who experience rapid growth. These conditions should be monitored during Increlex® treatment, if clinical symptoms such as limp, pain in the hip or knees occur.[3]

- **Hypersensitivity**

  Cases of hypersensitivity, urticaria, pruritus and erythema have been reported in patients treated with Increlex®, both as systemic and/or local injection site reactions. A small number of cases indicative of anaphylaxis and requiring hospitalisation have been reported. Patients and parents/caregivers should be informed that such reactions are possible and that if a systemic allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.[3]

- As with all protein-containing medicines, some patients may develop antibodies to Increlex®.

  No attenuation of growth has been observed in clinical trials as a consequence of the development of antibodies. Persons who have allergic reactions to injected IGF-1, who have unexpectedly high blood values of IGF-1 after injection or who fail to show a growth response without any identified cause may be having an antibody response to injected IGF-1. This may be through the production of anti-IGF-1 IgEs, sustaining antibodies or neutralising antibodies respectively. In such instances, antibody testing should be considered[4].

- Increlex® contains 9 mg/ml benzyl alcohol as preservative. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

- Increlex® is not recommended for use in children below the age of 2 years due to lack of data on safety and efficacy in this patient group.

- Overdosing may lead to supraphysiological IGF-1 levels and may increase the risk of benign and malignant neoplasm. Therefore, the maximum daily dose should not be exceeded.
  In case of an acute or a chronic overdose, Increlex must be discontinued immediately. If Increlex is restarted, the dose should not exceed the recommended daily dosage.

- Increlex is subject to additional monitoring as a condition of its marketing authorisation in Israel. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
  Adverse events can be reported to the Ministry of Health using the online form for adverse event reporting which can be found on the Ministry of Health website: www.health.gov.il or by using the following link: https://sideeffects.health.gov.il/.
  Adverse events can be also reported to Medison Pharma Ltd.
  by email: pv@medison.co.il or fax: 03- 9234218.

References

1. Backeljauw PF, Underwood LE. Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study. J Clin Endocrinol Metab 2001; 86:1504-1510.
2. Backeljauw PF, Chernausek SD. Treatment of Insulin-Like Growth Factor Deficiency with IGF-1: Studies in Humans. Horm Res 2006; 65 (Suppl 1): 21-27.
3. Increlex SmPC.

4. EMEA/H/C/704/SOB 001.7

Link to current PPI on Ministry of Health website:

https://mohpublic.z6.web.core.windows.net/IsraelDrugs/Rishum_16_359944120.pdf

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