BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The Applicant Tercica Europe Ltd. submitted on 7 December 2005 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for INCRELEX, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on Applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

INCRELEX was designated as an orphan medicinal product EU/3/06/373 on 22 May 2006. INCRELEX was designated as an orphan medicinal product in the following indication: Treatment of primary insulin-like growth factor-1 deficiency due to molecular or genetic defects. The calculated prevalence of this condition was less than 2 per 10.000 EU population. INCRELEX was also designated as an orphan medicinal product EU/3/05/307 on 26 August 2005 in the following indication: Treatment of primary growth hormone insensitivity syndrome. The calculated prevalence of this condition was not more than 1 in 10,000 EU population.

The Applicant applied for the following indication:

For the long-term treatment of growth failure in children with severe Primary insulin-like growth factor-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Severe Primary IGFD is defined by:

- height standard deviation score ≤ –3.0 and
- basal IGF-1 levels below the age- and gender-specific normal range and
- normal or elevated GH.

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.

INCRELEX is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating INCRELEX treatment.

INCRELEX is not a substitute for GH treatment

Information relating to Orphan Market Exclusivity

There are no other orphan medicinal products authorised in the Community in this same indication.

Scientific Advice:
The Applicant did not seek scientific advice at the CHMP.

Licensing status:
INCRELEX has been given a Marketing Authorisation in the United States of America on 30 August 2005.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pirjo Laitinen-Parkkonen** Co-Rapporteur: **János Borvendég**

2. Steps taken for the assessment of the product

- The application was received by the EMEA on 7 December 2005.
- The procedure started on 28 December 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 March 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 March 2006.
- During the meeting on 19-20 April 2006, the BWP discussed the consolidated list of quality questions and adopted a first report to the CHMP.
- During the meeting on 24-27 April 2006, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 27 April 2006.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 9 August 2006.
- GMP inspections of Cambrex BioSciences Baltimore, Inc. and Baxter Pharmaceutical Solutions LLC, Bloomington, USA were requested at the January 2006 CHMP meeting.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 26 September 2006.
- During the meeting on 9-11 October 2006, the BWP discussed the outstanding quality questions and adopted a second report to the CHMP.
- During the CHMP meeting on 16-19 October 2006, the CHMP agreed on a list of outstanding issues to be addressed in writing by the Applicant.
- During the meeting on 4-6 December 2006, the BWP clarified the outstanding issues and adopted a third report to the CHMP.
- The Applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 April 2007.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues on 10 May 2007.
- During the meeting on 14-16 May 2007, the BWP discussed the Applicant's responses to the List of outstanding issues and adopted a forth report to the CHMP.
- During the meeting on 21-24 May 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to INCRELEX on 24 May 2007.
- The Applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 22 May 2007.
- The Applicant notified the withdrawal of the indication referring to patients "with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH" as it did not fall within the scope of the orphan indication, on 29 May 2007.
- During the written procedure on 01-04 June 2007, the CHMP, in light of the overall data submitted, adopted a revised opinion recommending granting a Marketing Authorisation under exceptional circumstances to INCRELEX.
- The Applicant provided an updated letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 29 May 2007.