The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

26 June 2003
CPMP/3477/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 7(5) REFERAL

GENOTROPIN

International non-proprietary name (INN): **Somatropin**

BACKGROUND INFORMATION *

Genotropin, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth and by mobilisation of body fat. The first national Marketing Authorisation was granted in Denmark on 8 March 1988 and subsequently in all Member States.

On 22 November 2001, Germany and Sweden referred the matter to the EMEA under article 7(5) of Commission Regulation 541/95. Germany and Sweden considered that the data provided in the variations submitted by the Marketing Authorisation Holders to extend the indication to include children born small for gestational age (SGA) was not adequate to support the change requested as the limitation of the treatment period is likely to lead to high dose treatment and that a longer treatment time with a lower dose would be preferable, together with safety concerns regarding the increased risk at high doses for development of diabetes mellitus later in life.

The referral procedure started on 13 December 2001. The Rapporteur and Co-Rapporteur appointed were Dr. F. Lekkerkerker and Dr. P. Rossi, respectively. Written explanations were provided by the Marketing Authorisation Holders on 17 May 2002, 6 December 2002 and 25 February 2003.

Based on evaluation of the currently available data and the Rapporteurs' assessment reports, the CPMP considered that the benefit/risk profile of Genotropin in the indication "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 (HV SDS <0 during the last year) by 4 years of age or later" is favourable and therefore adopted on an opinion on 19 March 2003 recommending the variation to the Marketing Authorisations in accordance with the amended Summary of Product Characteristics.

The competent authorites of the Member States will continue to keep the product under regular review.

A list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II, together with the amended Summary of Product Characteristics in Annex III.

The final opinion was converted into a Decision by the European Commission on 26 June 2003.

* **Notes**: The information given in this document and Annexes reflect only the CPMP opinion dated 19 March 2003. The Member States competent authorities will continue to keep the product under regular review.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Austria	Pharmacia Austria GmbH, 1100 Wien	Genotropin 5,3 mg/ml KabiPen – Zylinderampullen	5,3 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	5
		Genotropin 12 mg/ml KabiPen – Zylinderampullen	12 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	5
		Genotropin 0,2 mg MiniQuick -Spritzampullen	0.2mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 0,4 mg MiniQuick -Spritzampullen	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 0,6 mg MiniQuick -Spritzampullen	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 0,8 mg MiniQuick -Spritzampullen	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 1 mg MiniQuick -Spritzampullen	1.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 1,2 mg MiniQuick -Spritzampullen	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 1,4 mg MiniQuick -Spritzampullen	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 1,6 mg MiniQuick -Spritzampullen	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 1,8 mg MiniQuick -Spritzampullen	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
		Genotropin 2 mg MiniQuick -Spritzampullen	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
Belgium/ Luxembourg	PHARMACIA NV/SA Rijksweg 12 2870 Puurs	Genotonorm 1,3 mg	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Vial + ampoule	1
		Genotonorm 5,0 mg	5.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5 5
		Genotonorm 5,3 mg	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5 5
		Genotonorm 12 mg	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotonorm 1,3 mg KabiVial	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1, 5
		Genotonorm 5,0 mg KabiVial	5.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 5,3 mg KabiVial	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 12 mg KabiVial	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm Miniquick 0,2 mg	0.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,4 mg	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
		Genotonorm Miniquick 0,6 mg	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,8 mg	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,0 mg	1.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,2 mg	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,4 mg	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,6 mg	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,8 mg	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 2,0 mg	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

Denmark	Pharmacia AS Overgaden neden Vandet 7 1414 Copenhagen K Denmark	Genotropin 1.3 mg	1.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Vial + ampoule	1
		Genotropin 0.7 mg KabiQuick	0.7mg/0.5 ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1 mg KabiQuick	1mg/0.75m l	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1.3 mg KabiQuick	1.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1.3 mg KabiVial	1.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1 5
		Genotropin 1.3 mg	1.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1
		Genotropin 5.0 mg KabiVial	5.0mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 5.0 mg	5.0mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5
		Genotropin 5.3 mg KabiVial	5.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 5.3 mg	5.3mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5
		Genotropin 12 mg KabiVial	12mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 12 mg	12mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5

		Genotropin MiniQuick 0.2 mg	0.2mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.4 mg	0.4mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.6 mg	0.6mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.8 mg	0.8mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.0 mg	1.0mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.2 mg	1.2mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4 7
		Genotropin MiniQuick 1.4 mg	1.4mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4 7
		Genotropin MiniQuick 1.6 mg	1.6mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4 7
		Genotropin MiniQuick 1.8 mg	1.8mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4 7
		Genotropin MiniQuick 2.0 mg	2.0mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4 7
Finland	Pharmacia Oy Rajatorpantie 41 C 01640 Vantaa	Genotropin 5 mg	5 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5
		Genotropin 12 mg	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5

France	PHARMACIA SAS 1, rue Antoine Lavoisier – 78280 GUYANCOURT	Genotonorm 1,3 mg/1 ml without preservative for Kabidevice	1,3 mg / 1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge (single dose container)	1 5
		Genotonorm 5 mg/1 ml with preservative	5 mg /1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm 5,3 mg/1 ml with preservative	5,3 mg/1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm 12 mg/1 ml with preservative	12 mg/1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm Kabivial 1,3 mg/1 ml without preservative	1,3 mg / 1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge (single dose container)	1 5
		Genotonorm Kabivial 5 mg/ 1 ml with preservative	5 mg /1ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm Kabivial 5,3 mg/1 ml with preservative	5,3 mg/1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm Kabivial 12 mg/ 1 ml with preservative	12 mg/1 ml	Powder and solvent for solution for injection in cartridge	Subcutaneous use	Cartridge	1 5
		Genotonorm Kabiquick 0,7 mg/0,5 ml	0,7 mg/0,5 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Cartridge (single dose container)	10
		Genotonorm Kabiquick 1 mg/0,75 ml	1 mg/0,75 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Cartridge (single dose container)	10
		Genotonorm Kabiquick 1,3 mg/1 ml	1,3 mg/1 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Cartridge (single dose container)	10

		Genotonorm Miniquick 0,2 mg/0,25 ml	0,2 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,4 mg/0,25 ml	0,4 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,6 mg/ 0,25 ml	0,6 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,8 mg/0,25 ml	0,8 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1 mg/0,25 ml	1 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,2 mg/0,25 ml	1,2 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,4 mg/0,25 ml	1,4 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,6 mg/0,25 ml	1,6 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,8 mg/0,25 ml	1,8 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7

		Genotonorm Miniquick 2 mg/0,25 ml	2 mg/0,25 ml	Powder and solvent for solution for injection in a prefilled syringe	Subcutaneous use	Injection syringe (single dose container)	7
Germany	Pharmacia GmbH 91051 Erlangen	Genotropin 1,3 mg	1.3 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container) or Vial + ampoule	1, 5 1, 10
		Genotropin 4 I.E. (1,3 mg) Multidose	1.3 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5
		Genotropin 5 mg/ml	5 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5, 4x5
		Genotropin 5,3 mg	5.3 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5, 4x5
		Genotropin 12 mg	12 mg/ml	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1 5
		Genotropin MiniQuick 0,2 mg	0.2 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 0,4 mg	0.4 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 0,6 mg	0.6 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 0,8 mg	0.8 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7

		Genotropin MiniQuick 1,0 mg	1.0 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 1,2 mg	1.2 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 1,4 mg	1.4 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 1,6 mg	1.6 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 1,8 mg	1.8 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
		Genotropin MiniQuick 2,0 mg	2.0 mg/0.25 ml	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7 4x7
Greece	Pharmacia Hellas S.A, 2 Kalavryton str., N. Kiffissia 14564, Athens, Greece	Genotropin	5.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10

		Genotropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1, 5
		Genotropin	0.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin	2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
Ireland	Pharmacia Laboratories Ltd Davy Avenue	Genotropin MiniQuick 0.2 mg	0.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

	Milton Keynes MK5 8PH	Genotropin MiniQuick 0.4 mg	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.6 mg	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.8 mg	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1 mg	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.2 mg	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1.4 mg	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1.6 mg	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1.8 mg	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 2.0 mg	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin 0.7 mg Kabiquick	0.7 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1 mg Kabiquick	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1.3 mg Kabiquick	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10

		Genotropin 1.3 mg	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1
		Genotropin 12 mg	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5mg Injection	5 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5mg Kabivial	5 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5.3 mg	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
Italy	Pharmacia AB Lindhagensgatan 133 SE-11287 Stockholm	Genotropin 0,7 mg Kabiquick	0.7 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1 mg Kabiquick	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	8
		Genotropin 1,3 mg Kabiquick	1.3.mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	6
		Genotropin 1,3 mg KabiVial	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1
		Genotropin 5,3 mg KabiVial	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 12 mg KabiVial	12.mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5,3 mg for Genotropin-Pen	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1

		Genotropin 12 mg for Genotropin-Mixer, Genotropin-Pen	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		enotropin MiniQuick 0,2mg	0,2mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		enotropin MiniQuick 0,4mg	0,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		enotropin MiniQuick 0,6mg	0,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		enotropin MiniQuick 0,8mg	0,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		enotropin MiniQuick 1mg	1.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		enotropin MiniQuick 1,2mg	1,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4
		enotropin MiniQuick 1,4mg	1,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4
		enotropin MiniQuick 1,6mg	1,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4
		enotropin MiniQuick 1,8mg	1,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4
		enotropin MiniQuick 2mg	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4
The Netherlands	Pharmacia B.V. Houttuinlaan 4 3447 GM Woerden	Genotropin 0,7mg KabiQuick	0,7mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10

		Genotropin 1mg KabiQuick	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1,3mg KabiQuick	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin 1,3mg KabiVial	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1, 5
		Genotropin 1,3mg	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1
		Genotropin5,0mg KabiVial	5,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5,0 mg	5,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5,3mg KabiVial	5,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 5,3mg	5,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 12mg	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5

		Genotropin MiniQuick 0,2mg	0,2mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0,4mg	0,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0,6mg	0,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0,8mg	0,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1mg	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1,2mg	1,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1,4mg	1,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1,6mg	1,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 1,8mg	1,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
		Genotropin MiniQuick 2mg	2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	4, 7
Portugal	Pharmacia Corporation Laboratórios, Lda. Av. do Forte, nº3 2795-505 CARNAXIDE Portugal	Genotropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Vial + ampoule	1

		Genotropin	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1, 5
		Genotropin	5.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin Kabi Vial	5.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin Kabi Vial	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin KabiQuick	0.7 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin KabiQuick	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin KabiQuick	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin Miniquick	0.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1

		Genotropin Miniquick	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	1.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
		Genotropin Miniquick	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	1
Spain	Pharmacia Spain, S.A.	Genotonorm 0,7 mg Kabiquick	0,7 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotonorm 1 mg Kabiquick	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotonorm 1,3 mg Kabiquick	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotonorm 1,3 Kabi vial s.c.	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	1, 5

		Genotonorm 1,3 mg Kabivial c.c.	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotonorm 5,3 mg Kabivial	5,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 5,3 mg Kabipen	5,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 12 mg Kabivial	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 12 mg Kabipen	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 5,0 mg Kabivial	5,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm 5,0 mg	5,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotonorm Miniquick 0,2 mg	0,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,4 mg	0,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,6 mg	0,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 0,8 mg	0,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1 mg	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

		Genotonorm Miniquick 1,2 mg	1,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,4 mg	1,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,6 mg	1,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 1,8 mg	1,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotonorm Miniquick 2 mg	2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
Sweden	Pharmacia Sverige AB	Genotropin Miniquick	0,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	0,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	0,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	0,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	1,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	1,2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	1,4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

		Genotropin Miniquick	1,6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	1,8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin Miniquick	2,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	5,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	5,0 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container) or Vial + ampoule	1, 10
		Genotropin (KabiQuick)	0,7 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin (KabiQuick)	1 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
		Genotropin (KabiQuick)	1,3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge (single dose container)	10
United Kingdom	Pharmacia Laboratories Ltd Davy Avenue Milton Keynes MK5 8PH	Genotropin MiniQuick 0.2 mg	0.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.4 mg	0.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7

		Genotropin MiniQuick 0.6 mg	0.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 0.8 mg	0.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.0 mg	1.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.2 mg	1.2 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.4 mg	1.4 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.6 mg	1.6 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 1.8 mg	1.8 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin MiniQuick 2.0 mg	2.0 mg	Powder and solvent for solution for injection	Subcutaneous use	Injection syringe (single dose container)	7
		Genotropin 12 mg	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 12 mg KabiVial Multidose	12 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1
		Genotropin 5 mg Injection	5 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5
		Genotropin 5 mg KabiVial	5 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1, 5

		Genotropin 1.3 mg	1.3 mg	Powder and solvent for solution for injection	Subcutaneous use	*Vial + ampoule*	1
		Genotropin 5.3 mg	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	*Cartridge*	1, 5
		Genotropin 5.3 mg KabiVial Multidose	5.3 mg	Powder and solvent for solution for injection	Subcutaneous use	Cartridge	1

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF GENOTROPIN AND RELATED NAMES (SEE ANNEX I)

Genotropin, which contains the active ingredient somatropin, is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat.

The variations submitted by the MAHs via the mutual recognition procedure were a proposal to extend the indication to include children born small for gestational age (SGA).

The RMS (Denmark) considered the variation approvable. A notification for referral according to Article 7(5) of Commission Regulation EC No. 541/95 was submitted by Germany and Sweden on 22 November 2001 based on concerns that the data were not adequate to support the change requested, as the limitation of the treatment period is likely to lead to high dose treatment and that a longer treatment time with a lower dose would be preferable, together with safety concerns regarding the increased risk at high doses for development of diabetes mellitus later in life.

On 13 December 2001, the CPMP asked the MAHs to provide data on the optimal age for initiating treatment and duration of GH therapy in SGA children, additional benefits besides increased height, as well as short-term and long-term consequences of treatment.

Efficacy

The clinical studies and published literature submitted demonstrate that the use of Genotropin is associated with improvements in predicted height SDS. However, there were insufficient data on (near) final height. Thus, no definite conclusion on the efficacy in the treatment of children born SGA could be reached. On the request of the CPMP, a meta-analysis was performed on patients that reached (near) final height.

This meta-analysis included 56 patients and provided important insights of the benefit of Genotropin for final height improvement in SGA children. The meta-analysis demonstrated a mean increase in height SDS of 1.90 for the 0.033 mg/kg/day dose (1.49-2.30 95% confidence intervals) and 2.19 SDS for the 0.067 mg/kg/day dose (1.85-2.53 95% confidence interval).

Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

The major issues discussed during the procedure were related to the patient population, the age for start of treatment, as well as posology and duration of treatment.

The criteria for the patient population were decided to be height SDS of <-2.5 and a HV SDS of < 0 during the last year. A starting age of 4 years was accepted by the CPMP because normal catch-up growth will occur before the age of 4 years.

The CPMP was of the opinion that the limited data in patients near puberty should lead to the advice not to initiate treatment in SGA patients near the onset of puberty.

Non-responders, expressed as patients with a height gain below the expected, should stop treatment for the lack of efficacy after the first year of treatment if the height velocity SDS is below + 1. Treatment should be stopped if the height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Safety

The data presented in the patient population does not support the existence of major unexpected risks during treatment.

The incidence of drug-related adverse events was low. The most frequently reported adverse events represented common childhood infections (viral infections, otitis media, pharyngitis, rhinitis, upper

respiratory tract infections). The more frequent reporting of such infections in GH treated children is considered coincidental and/or attributable to underreporting in untreated children.

There is no evidence that the musculo-skeletal events were related to an acromegalic effect of treatment and a warning for scoliosis is reflected in the current SPC for growth hormones.

In general, changes in glucose, insulin, IGF-I, and HbA1c values were not clinically significant, however they were indicative of a compensatory response of the pancreas to the reduction in insulin sensitivity induced by growth hormone. As high IGF-I levels were found in both treatment groups and as there is a lack of safety data on long-term high levels of IGF-I in children, a warning is introduced; if on repeated measurement, IGF-I levels exceed +2 SD compared to references for age and pubertal status, the IGF-I / IGFBP-3 ratio could be taken into account to consider dose adjustment. At the moment the data are reassuring considering the effects on glucose metabolism, but the management of these patients should follow accepted clinical practice and include safety monitoring of fasting insulin and blood glucose prior to treatment and annually during treatment. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed and if overt diabetes occurs, growth hormone should not be administered. Long-term follow-up on safety is considered necessary.

Overall conclusion on benefit/risk

At its meeting of 18-19 March 2003, the CPMP considered the data presented by the MAHs and reached the following conclusion.

From the data on efficacy, it has been shown that Genotropin is effective for the treatment of 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 (HV SDS <0 during the last year) by 4 years of age or later.

The short-term safety data related to the extended indication does not add any major unexpected risks and long-term safety data are necessary.

The MAHs committed to perform a post-marketing study to further investigate long-term metabolic effects after discontinuation of treatment in children born SGA.

On the basis of the efficacy data taking into account the concerns on long-term safety, the CPMP decided that the treatment should be initiated at a dose of 0.035 mg/kg/day and continued until final height is reached.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CPMP considered the referral made under article 7(5) of Commission Regulation EC No 541/95, for Genotropin and related invented names (see Annex I),
- the CPMP agreed that Genotropin is effective in the indication *"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 (HV SDS <0 during the last year) by 4 years of age or later",*
- no unexpected adverse events related to the extended indication were presented,
- the CPMP, as a consequence, considered the benefit/risk balance for the above-mentioned extension of indication to be favourable,

the CPMP has recommended the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Genotropin and related invented names (see Annex I).

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for Genotropin and related names. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Invented name>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin (INN), recombinant DNA-derived human growth hormone produced in E.coli.

<To be completed as appropriate>

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection. In the two-chamber cartridge there is a white powder in the front compartment and a clear solution in the rear compartment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children
Growth disturbance due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome or chronic renal insufficiency.
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 (HV SDS < 0 during the last year) by 4 years of age or later.
Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults
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 prolaction. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone 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.

4.2 Posology and method of administration

The dosage and administration schedule should be individualized.

The injection should be given subcutaneously and the site varied to prevent lipoatrophy.

Growth disturbance due to insufficient secretion of growth hormone in children: Generally a dose of 0.025 - 0.035 mg/kg body weight per day or 0.7 - 1.0 mg/m² body surface area per day is recommended. Even higher doses have been used.

Prader-Willi syndrome, for improvement of growth and body composition in children: Generally a dose of 0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day is recommended. Daily doses of 2.7 mg should not be exceeded. Treatment should not be used in children with a growth velocity less than 1 cm per year and near closure of epiphyses.

Growth disturbance due to Turner syndrome: A dose of 0.045 - 0.050 mg/kg body weight per day or 1.4 mg/m² body surface area per day is recommended.

Growth disturbance in chronic renal insufficiency: A dose of 1.4 mg/ m² body surface area per day (approximately 0.045 - 0.050 mg/kg body weight per day) is recommended. Higher doses can be needed if growth velocity is too low. A dose correction can be needed after six months of treatment.

Growth disturbance in short children born small for gestational age (SGA): A dose of 0.035 mg/kg body weight per day (1 mg/m² body surface area per day) is usually recommended until final height is reached (see section 5.1). Treatment should be discontinued after the first year of treatment if the height velocity SDS is below + 1. Treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Dosage recommendations for Pediatric Patients

Indication	mg/kg body weight dose per day	mg/m² body surface area dose per day
Growth hormone deficiency in children	0.025 - 0.035	0.7 - 1.0
Prader-Willi syndrome in children	0.035	1.0
Turner syndrome	0.045 - 0.050	1.4
Chronic renal insufficiency	0.045 - 0.050	1.4
Children born small for gestational age (SGA)	0.035	1.0

Growth hormone deficient adult patients: Therapy should start with a low dose, 0.15 – 0.3 mg per day. The dose should be gradually increased according to individual patient requirements as determined by the IGF-I concentration. Treatment goal should be insulin-like growth factor (IGF-I) concentrations within 2 SDS from the age corrected mean. Patients with normal IGF-I concentrations at the start of the treatment should be administered growth hormone up to an IGF-I level into upper range of normal, not exceeding the 2 SDS. Clinical response and side effects may also be used as guidance for dose titration. The daily maintenance dose seldom exceeds 1.0 mg per day**.** Woman may require higher doses than men, with men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are under-treated while men are over-treated. The accuracy of the growth hormone dose should therefore be controlled every 6 months. As normal physiological growth hormone production decreases with age, dose requirements may be reduced. The minimum effective dose should be used.

4.3 Contraindications

<*Invented name*> should not be used when there is any evidence of tumour activity and anti-tumour therapy must be completed prior to starting therapy.

<*Invented name*> should not be used for growth promotion in children with closed epiphyses.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with <*Invented name*>. (Regarding patients undergoing substitution therapy, see 4.4 “Special warnings and special precautions for use”.)

4.4 Special warnings and special precautions for use

Diagnosis and therapy with <*Invented name*> should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with the therapeutic indication of use.

Note: Not applicable to Miniquick
Myositis is a very rare adverse event that may be related to the preservative m-cresol. In the case of myalgia or disproportionate pain at injection site, myositis should be considered and if confirmed, a <*Invented name*> presentation without m-cresol should be used.

Somatropin may induce a state of insulin resistance and in some patients hyperglycaemia. Therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria for diabetes mellitus type II may be fulfilled as a result of the somatropin therapy, but risk factors such as obesity (including obese PWS patients), family history, steroid treatment, or pre-existing impaired glucose tolerance have been present in most cases where this have occurred. In patients with an already manifest diabetes mellitus, the anti-diabetic therapy might require adjustment when somatropin is instituted.

During treatment with somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In general, the peripheral thyroid hormone levels have remained within the reference ranges for healthy subjects. The effects of somatropin on thyroid hormone levels may be of clinical relevance in patients with central subclinical hypothyroidism in whom hypothyroidism theoretically may develop. Conversely, in patients receiving replacement therapy with thyroxin mild hyperthyroidism may occur. It is therefore particularly advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

In growth hormone deficiency secondary to treatment of malignant disease, it is recommended to pay attention to signs of relapse of the malignancy.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. Children limping during treatment with somatropin, should be examined clinically.

In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued. At present there is insufficient evidence to give specific advice on the continuation of growth hormone treatment in patients with resolved intracranial hypertension. However, clinical experience has shown that reinstitution of the therapy is often possible without recurrence of the intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Experience in patients above 60 years is limited.

In patients with PWS, treatment should always be in combination with a calorie-restricted diet.

Scoliosis is common in patients with PWS. Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

Experience with prolonged treatment in adults and in patients with PWS is limited.

In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

In SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

In SGA children it is recommended to measure the IGF-I level before start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels exceed +2 SD compared to references for age and pubertal status, the IGF-I / IGFBP-3 ratio could be taken into account to consider dose adjustment.

Experience in initiating treatment in SGA patients near onset of puberty is limited. It is therefore not recommended to initiate treatment near onset of puberty. Experience in patients with Silver-Russell syndrome is limited.

Some of the height gain obtained with treating short children born SGA with growth hormone may be lost if treatment is stopped before final height is reached.

In chronic renal insufficiency, renal function should be below 50 percent of normal before institution of therapy. To verify growth disturbance, growth should be followed for a year preceding institution of therapy. During this period, conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism and nutritional status) should have been established and should be maintained during treatment.
The treatment should be discontinued at renal transplantation.
To date, no data on final height in patients with chronic renal insufficiency treated with <*Invented name*> are available.

The effects of <*Invented name*> on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg <*Invented name*> daily compared to patients receiving placebo, 42% vs. 19%. Based on this information, these types of patients should not be treated with <*Invented name*>. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.
In all patients developing other or similar acute critical illness, the possible benefit of treatment with <*Invented name*> must be weighed against the potential risk involved.

4.5 Interaction with other medicinal products and other forms of interaction

Data from an interaction study performed in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.
Also see section 4.4 for statements regarding diabetes mellitus and thyroid disorder and section 4.2 for statement on oral oestrogen replacement therapy.

4.6 Pregnancy and lactation

No clinical experience of use in pregnant women is available. Animal experimental data are incomplete. Treatment with <*Invented name*> should be interrupted if pregnancy occurs.

During normal pregnancy levels of pituitary growth hormone fall markedly after 20 gestation weeks, being replaced almost entirely by placental growth hormone by 30 weeks. In view of this, it is unlikely that continued replacement therapy with somatropin would be necessary in growth hormone deficient women in the third trimester of pregnancy.

It is not known if somatropin is excreted into breast milk, but absorption of intact protein from the gastrointestinal tract of the infant is extremely unlikely.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Patients with growth hormone deficiency are characterised by extracellular volume deficit. When treatment with somatropin is started this deficit is rapidly corrected. In adult patients adverse effects related to fluid retention, such as peripheral oedema, stiffness in the extremities, arthralgia, myalgia and paraesthesia are common. In general these adverse effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose-reduction.

The incidence of these undesirable effects is related to the administered dose, the age of patients, and possibly inversely related to the age of patients at the onset of growth hormone deficiency. In children such adverse effects are uncommon.

Transient local skin reactions at the injection site in children are common.

Rare cases of diabetes mellitus type II have been reported.

Rare cases of benign intracranial hypertension have been reported.

Carpal tunnel syndrome is an uncommon event among adults.

Somatropin has given rise to the formation of antibodies in approximately 1 % of the patients. The binding capacity of these antibodies has been low and no clinical changes have been associated with their formation.

Neoplasms, benign and malignant
Very rare (<1/10 000): Leukemia.

Immune system disorders
Common (>1/100, <1/10): Formation of anitibodies.

Endocrine disorders
Rare (>10 000, <1/1000): Diabetes mellitus type II.

Nervous system disorders
Common (>1/100, <1/10): In adults paraesthesia.
Uncommon (>1/1000, <1/100): **In adults carpal tunnel syndrome; In children paraesthesia.**
Rare (>10 000, <1/1000): Benign intracranial hypertension.

Skin and subcutaneous tissue disorders
Common (>1/100, <1/10): In children transient local skin reactions.

Musculoskeletal, connective tissue and bone disorders
Common (>1/100, <1/10): In adults stiffness in the extremities, arthralgia, myalgia.
Uncommon (>1/1000, <1/100): In children stiffness in the extremities, arthralgia, myalgia.

General disorders and administration site disorders
Common (>1/100, <1/10): In adults peripheral oedema.
Uncommon (>1/1000, <1/100): In children peripheral oedema.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increased hepatic clearance. The clinical relevance of these findings may be limited. Nevertheless, corticosteroid replacement therapy should be optimised before initiation of <*Invented name*> therapy.

Very rare cases of leukemia have been reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.

4.9 Overdose

No case of overdose or intoxication has been reported.
Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia.
Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: H01A C01

Somatropin is a potent metabolic hormone of importance for the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilization of body fat. Visceral adipose tissue is particularly responsive to somatropin. In addition to enhanced lipolysis, somatropin decreases the uptake of triglycerides into body fat stores. Serum concentrations of IGF-I (Insulin-like Growth Factor-I), and IGFBP3 (Insulin-like Growth Factor Binding Protein 3) are increased by somatropin. In addition, the following actions have been demonstrated:

- Lipid metabolism: Somatropin induces hepatic LDL cholesterol receptors, and affects the profile of serum lipids and lipoproteins. In general, administration of somatropin to growth hormone deficient patients results in reductions in serum LDL and apolipoprotein B. A reduction in serum total cholesterol may also be observed.

- Carbohydrate metabolism: Somatropin increases insulin but fasting blood glucose is commonly unchanged. Children with hypopituitarism may experience fasting hypoglycaemia. This condition is reversed by somatropin.

- Water and mineral metabolism: Growth hormone deficiency is associated with decreased plasma and extracellular volumes. Both are rapidly increased after treatment with somatropin. Somatropin induces the retention of sodium, potassium and phosphorus.

- Bone metabolism: Somatropin stimulates the turnover of skeletal bone. Long-term administration of somatropin to growth hormone deficient patients with osteopenia results in an increase in bone mineral content and density at weight-bearing sites.

- Physical capacity: Muscle strength and physical exercise capacity are improved after long-term treatment with somatropin. Somatropin also increases cardiac output, but the mechanism has yet to be clarified. A decrease in peripheral vascular resistance may contribute to this effect.

In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of subcutaneously administered somatropin is approximately 80 % in both healthy subjects and growth hormone deficient patients. A subcutaneous dose of 0.035 mg/kg of somatropin results in plasma C_{max} and t_{max} values in the range of 13-35 ng/ml and 3-6 hours respectively.

Elimination
The mean terminal half-life of somatropin after intravenous administration in growth hormone deficient adults is about 0.4 hours. However, after subcutaneous administration, half-lives of 2-3 hours are achieved. The observed difference is likely due to slow absorption from the injection site following subcutaneous administration.

Sub-populations
The absolute bioavailability of somatropin seems to be similar in males and females following s.c. administration.

Information about the pharmacokinetics of somatropin in geriatric and pediatric populations, in different races and in patients with renal, hepatic or cardiac insufficiency is either lacking or incomplete.

5.3 Preclinical safety data

In studies regarding general toxicity, local tolerance and reproduction toxicity no clinically relevant effects have been observed.
In vitro and in vivo genotoxicity studies on gene mutations and induction of chromosome aberrations have been negative.

An increased chromosome fragility has been observed in one in-vitro study on lymphocytes taken from patients after long term treatment with somatropin and following the addition of the radiomimetic drug bleomycin. The clinical significance of this finding is unclear.

In another study, no increase in chromosomal abnormalities was found in the lymphocytes of patients who had received long term somatropin therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<To be completed as appropriate>

6.2 Incompatibilities

<To be completed as appropriate>

6.3 Shelf life

<To be completed as appropriate>

6.4 Special precautions for storage

<To be completed as appropriate>

6.5 Nature and contents of container

<To be completed as appropriate>

6.6 Instructions for use and handling

<To be completed as appropriate>

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

