NutropinAq

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/03/2022		PL	
PSUSA/2772/ 202003	Periodic Safety Update EU Single assessment - somatropin	10/12/2020	18/02/2021	SmPC and PL	In view of available data on risk(s) from clinical trial(s), the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

					re-challenge, the PRAC Rapporteur considers a causal relationship between somatropin and acute pancreatitis is at least a reasonable possibility. The PRAC Rapporteur concludes that Section 4.4 of the SmPC of products containing somatropin should be amended to add a warning on pancreatitis. Additionally, the PRAC Rapporteur considers a causal relationship between somatropin and gynecomastia is established and concludes that section 4.8 of the SmPC of products containing somatropin should be amended, to add the adverse reaction gynecomastia with a frequency uncommon. The Package leaflet is updated accordingly.
IA/0075	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2020	n/a		
IB/0073	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/04/2020	n/a		
IA/0072	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/01/2020	18/02/2021	SmPC, Annex II, Labelling and PL	
IA/0071	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/09/2018	23/08/2019	SmPC, Annex II, Labelling and PL	
IA/0070	A.7 - Administrative change - Deletion of manufacturing sites	23/05/2018	n/a		

II/0069/G	This was an application for a group of variations. II: C.I.11: Submission of an updated RMP version 3.0 in order to include formatting in accordance with the new RMP template and to include updates from the post-approval safety study (PASS) International Cooperative Growth Study (iNCGS) Post Marketing Surveillance Program For NutropinAq. II: C.I.13: Submission of the final report from International Cooperative Growth Study (iNCGS) Post Marketing Surveillance Program For NutropinAq. This study collected long-term safety and effectiveness data on NutropinAq during treatment of paediatric growth disorders for which growth hormone is indicated. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/04/2018	n/a		
PSUSA/2772/201703	Periodic Safety Update EU Single assessment - somatropin	14/12/2017	22/02/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2772/201703.
II/0068/G	This was an application for a group of variations. B.II.b.2.b) To add Roche Pharma AG, Emil-Barell-Strasse 1, Grenzach-Wyhlen, Baden-Wuerttemberg, 79639, Germany as an alternative site for the quality	23/11/2017	n/a		

	control of the test parameter of potency by the cell proliferation assay of the finished product NutropinAq 10mg/2ml solution for injection. B.II.d.2.d) Minor changes to the test procedure of cell proliferation assay for the finished product to incorporate enhanced system suitability to determine the potency of a sample by full-curve parallel line analysis using dose-response curves generated for the samples and standards. B.I.b.2.e) Minor changes to the test procedure of cell proliferation assay for the active substance Somatropin to incorporate enhanced system suitability to determine the potency of a sample by full-curve parallel line analysis using dose-response curves generated for the samples and standards. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				

IB/0066/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/05/2017	n/a		
II/0065	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	13/10/2016	n/a		
PSUSA/2772/ 201509	Periodic Safety Update EU Single assessment - somatropin	13/05/2016	n/a		PRAC Recommendation - maintenance
IB/0064	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	27/04/2016	n/a		
IB/0063	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/03/2016	n/a		
II/0061/G	This was an application for a group of variations.	25/02/2016	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0060	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	07/01/2016	n/a		
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2015	22/02/2018	PL	
IA/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	09/12/2015	n/a		
II/0056/G	This was an application for a group of variations. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing	24/09/2015	n/a		

	process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				

IAIN/0057	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	02/02/2015	n/a		
PSUSA/2772/ 201403	Periodic Safety Update EU Single assessment - somatropin	06/11/2014	n/a		PRAC Recommendation - maintenance
IAIN/0054	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/07/2014	n/a		
IA/0053/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	09/12/2013	n/a		

	product - Minor changes to an approved test procedure				
IB/0052	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	29/11/2013	n/a		
IA/0051/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	21/11/2013	n/a		
IA/0049	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/06/2013	n/a		
II/0048	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	06/05/2014	SmPC, Annex II, Labelling and PL	
II/0043/G	This was an application for a group of variations. Additional site for the manufacture and quality	21/06/2012	21/06/2012		

	control of the finished product B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IB/0047	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	07/05/2012	n/a		
IB/0046	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	04/05/2012	n/a		
IB/0045	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	04/05/2012	n/a		

IB/0044	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	04/05/2012	n/a		
IA/0042	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	02/03/2012	n/a		
A20/0040	Article 20 Review On 10 December 2010, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for somatropin-containing medicinal products authorised in the centralised procedure and requested the CHMP to assess all the available data and its impact on the risk benefit balance for somatropin-containing medicinal products and to give its opinion on measures necessary to ensure the safe and effective use of these medicinal products and whether the marketing authorisations for these products should be maintained, varied, suspended or revoked. The scope of the review was to assess the long-term safety of growth hormone treatments in light of the emerging safety data from the French SAGHE study in particular with regards the potential increased risk of mortality due to diseases of the circulatory system, bone tumours and subarachnoid or intracerebral haemorrhage in children and when high	15/12/2011	02/03/2012	SmPC, Annex II and PL	Please refer to the Assessment Report: NutropinAq-H-315-A20-40-Assessment Report-Article 20.

	doses are used.				
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/05/2011	n/a	PL	
II/0038	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	14/04/2011	SmPC and PL	
II/0039	This type II variation concerned an update of section 4.5 of the SPC to add information regarding patients with adrenal insufficiency, interaction between somatropin and glucocorticoid replacement therapy and to add a minor clarification regarding Cytochrome P450. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC and PL	
II/0032	Changes to the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	21/10/2010	08/11/2010		

II/0033	Additional site for the storage of cell banks and raw materials B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	22/07/2010	28/07/2010		
IB/0037	To change in the stability programm of the active substance. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	19/07/2010	n/a		
IB/0034	Changes to the control of the drug substance B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	31/05/2010	n/a		
IA/0036	Change in the control of the active substance B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	21/05/2010	n/a		
IA/0035	Change to the manufacturing process of the drug	20/05/2010	n/a		

	substance B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2009	n/a	Labelling and PL	
T/0030	Transfer of Marketing Authorisation	03/07/2009	29/07/2009	SmPC, Labelling and PL	Transfer of Marketing Authorisation for NutropinAq from Ipsen Limited to Ipsen Pharma.
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/01/2009	n/a	PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/04/2008	n/a	PL	
IA/0027	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/03/2007	n/a		
II/0025	This variation refers to an update of section 4.4 ''Special warnings and precautions for use'' of the Summary of Product Characteristics to add a warning on aceptic necrosis in children with advanced renal osteodystrophy and in growth hormone deficiency. Update of Summary of Product Characteristics	21/09/2006	30/10/2006	SmPC	The MAH was requested to submit an overview of adverse reports on aseptic necrosis. Based on the available information, the CHMP considered that it is difficult to assess the relationship between reported cases of aseptic necrosis and therapy with growth hormone, since these events are very rare (< 0,01 %), and since this complication is more prevalent in children with chronic renal failure and growth hormone deficiency even without therapy. Nevertheless, the CHMP considered relevant to include the following warning in the SPC:

					''Patients with growth hormone failure secondary to CRI should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphyses and aseptic necrosis of the femoral head may be seen in children with advanced renal osteodystrophy and in growth hormone deficiency, and it is uncertain whether these problems are affected by GH therapy. Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in patients treated with somatropin".
II/0026	Change(s) to the test method(s) and/or specifications for the finished product	21/09/2006	27/09/2006		
II/0023	Change(s) to the test method(s) and/or specifications for the finished product	27/04/2006	05/05/2006		
R/0021	Renewal of the marketing authorisation.	26/01/2006	21/03/2006	SmPC, Annex II, Labelling and PL	
IA/0022	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	28/10/2005	n/a		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2005	n/a	PL	
II/0014	Change(s) to the manufacturing process for the active substance	21/04/2005	02/05/2005		
II/0012	Change(s) to the manufacturing process for the finished product	21/04/2005	02/05/2005		

II/0010	Change(s) to the test method(s) and/or specifications for the active substance	21/04/2005	02/05/2005		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/03/2005	n/a	Labelling and PL	
II/0013	Change(s) to the test method(s) and/or specifications for the active substance	17/02/2005	25/02/2005		
II/0011	Quality changes	17/02/2005	25/02/2005		
IB/0017	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	21/12/2004	n/a		
II/0009	Update of section 4.4 of SPC and relevant section of the PL following the assessment of the 5th PSUR. Update of Summary of Product Characteristics and Package Leaflet	21/10/2004	06/12/2004	SmPC and PL	The SPC and PL were updated with warning stating that Nutropin Aq is not indicated for the long term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome, unless they also have a diagnosis of growth hormone deficiency. It was also highlighted that there have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.
IA/0008	IA_47_c_Deletion of a pack size(s)	02/09/2004	n/a	SmPC, Labelling and PL	
N/0007	Minor change in labelling or package leaflet not	20/08/2004	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0006	New presentation(s)	21/01/2004	19/03/2004	SmPC, Labelling and PL	
II/0005	Change(s) to the test method(s) and/or specifications for the finished product	25/09/2003	30/09/2003		
I/0004	17_Change in specification of the medicinal product	04/08/2003	20/08/2003		
I/0003	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	05/06/2003	18/07/2003	Annex II and PL	
T/0002	Transfer of Marketing Authorisation	30/01/2003	24/02/2003	SmPC, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/11/2002	18/12/2002	PL	