Translarna

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
II/0036	UUpdate of section 4.5 of the SmPC in order to include information regarding the effects of ataluren on the pharmacokinetics of sensitive probe substrate of organic anion transporter 3 (OAT3)) following results from study PTC124-GD-037-HV (MEA015). In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce some editorial changes in the PI.	14/09/2017		SmPC, Labelling and PL	Caution should also be exercised when ataluren is co-administered with OAT3 substrates (eg, ciprofloxacin), especially those OAT3 substrates with a narrow therapeutic window. In a clinical study, the extent of exposure for ciprofloxacin was 32% higher in the presence of ataluren.

[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).

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	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10274 /201701	Periodic Safety Update EU Single assessment - ataluren	01/09/2017	n/a		PRAC Recommendation - maintenance
R/0032	Renewal of the marketing authorisation.	21/04/2017	16/06/2017		
IB/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/05/2017	n/a		
IAIN/0035/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	23/05/2017		SmPC, Annex II, Labelling and PL	
II/0031	Update of section 4.5 of the SmPC in order to introduce a new warning on interaction with adefovir based on results from study “Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 1 (OAT1)” (MEA014). The MAH took the occasion to correct minor typographical errors in the product information and to bring the PI in line with the QRD version 9.1.	23/03/2017	16/06/2017	SmPC, Annex II and PL	In a clinical study, the extent of exposure for adefovir was 60% higher in the presence of ataluren. Caution should be exercised when ataluren is co-administered with adefovir.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10274 /201607	Periodic Safety Update EU Single assessment - ataluren	09/02/2017	n/a		PRAC Recommendation - maintenance
II/0027	Update of section 4.8 of the SmPC to add that the safety profile of ataluren in non-ambulatory patients was similar to the safety profile in ambulatory patients to reflect the results of a 48-week open label extension study in patients with nonsense mutation Duchenne Muscular Dystrophy (nmDMD). The RMP is updated accordingly (version 6.3). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	16/06/2017	SmPC	In a 48-week open-label extension study in patients with nmDMD patients who were ambulant or non-ambulant demonstrated a similar safety profile. Long term safety data is not available.
R/0022	Renewal of the marketing authorisation.	23/11/2016	09/01/2017	Annex II	The CHMP, having reviewed the totality of the clinical data available including the final results of the study 020, is of the opinion that these continued to support the positive benefit-risk balance of Translarna in the context of a conditional approval. As a result of the annual renewal assessment, the specific obligation is revised as follows: In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH should conduct and submit the results of a two-phase multicentre, randomised study, including a double-blind, 18-month, placebo-controlled study, followed by a 18-month open label extension, according to an agreed

					protocol; (Final study report to be submitted: September 2021). Please refer to the assessment report for further details.
II/0016/G	This was an application for a group of variations. Update of section 4.4 to remove precautions for use relating to the co-administration of ataluren with substrates of UGT1A9 and section 4.5 of the SmPC to remove statements relating to the potential effect of co-administration of ataluren with substrates of UGT1A9 and to add results from studies PTC124-GD-026-HV and PTC124-GD-027-HV (MEA 011 and MEA 012). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC. Moreover, the updated RMP version 4.2.2 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	16/06/2017	SmPC and PL	n/a
IB/0030/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a	14/12/2016	n/a		

	manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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 B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits 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.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the				

	dossier) - Replacement or addition of a supplier				
II/0020	Update of sections 4.4, 4.8, 5.1 and 5.3 of the SmPC in order to reflect the results from the submitted study TC124-GD-020-DMD object of the specific obligation (SOB 001) for the conditional marketing authorisation. The Package Leaflet and the RMP are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to include some minor editorial changes throughout the Product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/11/2016	09/01/2017	SmPC and PL	The efficacy and safety of Translarna were assessed in 2 randomised, double-blind, placebo controlled, trials in nmDMD. The primary efficacy endpoint in both trials was change in 6 Minute Walk Distance (6MWD) at Week 48. Other endpoints included in both trials were time to persistent 10% worsening in 6MWD, change in time to run/walk 10 meters at Week 48, change in time to climb 4 stairs at Week 48, and change in time to descend 4 stairs at Week 48. Study 2 evaluated 230 male patients, ages 7 to 14 years. Ataluren-treated patients experienced clinical benefit as measured by numerically favorable differences versus placebo across the primary and secondary efficacy endpoints. As the primary endpoint (change in 6MWD from baseline to Week 48) did not reach statistical significance ($p \leq 0.05$), all other p values should be considered nominal. Separation between ataluren and placebo was maintained from Week 16 through the end of the study. The most common adverse reactions in the 2 placebo-controlled studies were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in ≥5% of all ataluren-treated patients. Lipid levels shifted from normal at baseline to high (above the upper limit of normal) at Week 48 in slightly higher percentages of patients receiving ataluren compared to those receiving placebo (total cholesterol 15.1% vs. 6.1%, triglycerides 21.1% vs. 13.4%, respectively). In both studies, 1/232 (0.43%) patients treated with ataluren discontinued due to an adverse reaction of constipation and 1/172 (0.58%) placebo patients discontinued treatment due to an adverse reaction of disease progression (loss of ambulation). Adverse

					reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these 2 studies.
II/0026	Update of sections 4.4 and 4.5 of the SmPC to remove the interaction with inhibitors of breast cancer resistant protein (BCRP) based on the results of a drug-drug interaction study of the co-administration of ataluren and inhibitors of BCRP. The package leaflet and the RMP (version 6.2) are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	09/01/2017	SmPC and PL	n/a
IAIN/0028/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/10/2016	n/a		
PSUSA/10274 /201601	Periodic Safety Update EU Single assessment - ataluren	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0025	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/06/2016	n/a		
II/0019	C.I.13 - Other variations not specifically covered	26/05/2016	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0024/G	This was an application for a group of variations. B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/05/2016	n/a		
PSUSA/10274 /201507	Periodic Safety Update EU Single assessment - ataluren	11/02/2016	n/a		PRAC Recommendation - maintenance
IAIN/0021	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	08/02/2016	n/a		
IB/0018	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/12/2015	n/a		
IA/0017	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/12/2015	n/a		
IB/0013/G	This was an application for a group of variations.	01/12/2015	n/a		

	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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IB/0015	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/11/2015	11/11/2016	SmPC	
PSUSA/10274 /201501	Periodic Safety Update EU Single assessment - ataluren	10/09/2015	n/a		PRAC Recommendation - maintenance
R/0007	Renewal of the marketing authorisation.	21/05/2015	28/07/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Translarna, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IAIN/0011	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	16/07/2015	n/a		
II/0005/G	This was an application for a group of variations. Submission of non-clinical study 100011749 (Study of Ataluren (PTC124) and M4 metabolite in the β3 binding assay) and non-clinical study 100012124	25/06/2015	n/a		

	(Study of ataluren (PTC124) and M4 (PTC-0256858-04) functional activity in a beta-3 adrenergic cellular assay) in fulfilment of MEA006; the RMP is updated accordingly (version 3.0). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0008/G	This was an application for a group of variations. 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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/06/2015	n/a		
IAIN/0010	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	21/05/2015	n/a		
IB/0006/G	This was an application for a group of variations. 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.11.z - Introduction of, or change(s) to, the	05/05/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IAIN/0003	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/01/2015	28/07/2015	SmPC	
IA/0004	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	22/01/2015	n/a		
IAIN/0002	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/11/2014	n/a		
T/0001	Transfer of Marketing Authorisation	22/09/2014	10/10/2014	SmPC, Labelling and PL	