EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

INOmax

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/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/04/2023		PL	
IA/0065	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate	22/11/2022	n/a		

[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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	from an already approved manufacturer				
PSUSA/2172/ 202112	Periodic Safety Update EU Single assessment - nitric oxide	01/09/2022	n/a		PRAC Recommendation - maintenance
IB/0063/G	This was an application for a group of variations. 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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	05/08/2021	n/a		
IA/0062	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	28/05/2021	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/10/2020	19/02/2021	PL	
IAIN/0060	A.1 - Administrative change - Change in the name and/or address of the MAH	08/05/2020	19/02/2021	SmPC, Labelling and PL	

IB/0058	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2020	19/02/2021	SmPC, Labelling and PL	
IA/0059	A.7 - Administrative change - Deletion of manufacturing sites	14/01/2020	n/a		
IB/0057	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	22/11/2019	n/a		
PSUSA/2172/ 201812	Periodic Safety Update EU Single assessment - nitric oxide	11/07/2019	n/a		PRAC Recommendation - maintenance
IA/0055	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/10/2018	n/a		
II/0051	B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging	22/03/2018	11/03/2019	SmPC, Labelling and PL	
IB/0054/G	This was an application for a group of variations. 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.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	15/02/2018	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
PSUSA/2172/ 201706	Periodic Safety Update EU Single assessment - nitric oxide	08/02/2018	n/a		PRAC Recommendation - maintenance
IA/0053	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	04/10/2017	n/a		
IB/0049	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	19/05/2017	n/a		
IA/0050	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	24/03/2017	n/a		
PSUSA/2172/ 201606	Periodic Safety Update EU Single assessment - nitric oxide	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/08/2016	16/02/2017	SmPC, Labelling and PL	
IAIN/0046	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/03/2016	16/02/2017	Annex II and PL	

PSUSA/2172/201506	Periodic Safety Update EU Single assessment - nitric oxide	14/01/2016	n/a		PRAC Recommendation - maintenance
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2015	16/02/2017	PL	
IA/0044	B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	12/11/2015	n/a		
PSUSA/2172/201412	Periodic Safety Update EU Single assessment - nitric oxide	10/09/2015	n/a		PRAC Recommendation - maintenance
IAIN/0042	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	16/07/2015	n/a		
PSUSA/2172/201406	Periodic Safety Update EU Single assessment - nitric oxide	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0039	Submission of an updated RMP for INOmax and update of Annex II to no longer require that the educational material for Healthcare Professionals should be 'a pocket size guide' In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH made minor editorial corrections and brought the PI in line with the latest QRD template version.	25/09/2014	18/09/2015	SmPC, Annex II and PL	

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/2172/ 201312	Periodic Safety Update EU Single assessment - nitric oxide	10/07/2014	n/a		PRAC Recommendation - maintenance
PSUSA/2172/ 201306	Periodic Safety Update EU Single assessment - nitric oxide	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0036	Update of section 5.3 of the SmPC "Preclinical safety data" to remove the risk of uterine adenocarcinomas further to the review of the results of the toxicity and carcinogenicity study in rats (study N0055243), previously assessed by the CHMP. The MAH also took the opportunity to update the contact information of several local representatives in the Package Leaflet, including the Croatian local representative. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	16/01/2014	SmPC and PL	A further review of a 2-year carcinogenicity study in rats performed in 2006, as well as the review of historical data across a number of published carcinogenicity studies and the NTP publically available historical control data, support the conclusion that none of the uterine lesions observed were considered to be related to NO exposure. The most likely explanation is that it is a spontaneous lesion. In terms of biological plausibility, there is no clear mechanism that would suggest a role of NO in epithelial uterine neoplasia, with biological effects more clearly related to smooth muscle. Therefore, section 5.3 of the SmPC is being updated to reflect that in the 2-year carcinogenicity study no evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 h/day for up to two years, and that higher exposures have not been investigated.

IB/0035	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 currently approved batch size	17/05/2013	n/a		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/04/2013	16/01/2014	PL	Update of the Slovakian local representative's address in the Package Leaflet. The MAH also took the opportunity to add previously missing addresses in the list of local representatives in the Bulgarian Package Leaflet.
II/0030	Update of the adverse events table in section 4.8 of the SmPC following a review of the safety data derived from the CNRGI pivotal study in term/near-term neonates and post-marketing safety surveillance, as requested by the CHMP. Update of the relevant sections of the package leaflet accordingly. Moreover a statement was added in section 6.6 'Special precautions for disposal and other handling' of the SmPC regarding the disposal of INOmax. Additionally, the product information has been updated with some minor linguistic amendments and in accordance with the latest QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/01/2013	16/01/2014	SmPC, Annex II, Labelling and PL	Further to the review of the safety data derived from the CNRGI pivotal study in term/near term neonates and post-marketing surveillance and post-marketing safety surveillance, the tabulated list of adverse reactions has been updated to more accurately reflect adverse drug reactions, adjust frequencies to also consider the increased number of exposed patients (from 300,000 to 482,585 subjects) and comply with the latest relevant guidelines and templates. 'Hypokalemia', and 'hyperbilirubinemia' have been removed from section 4.8 of the SmPC as these are not considered to be associated with the use of INOmax and 'bradycardia' (following abrupt discontinuation of therapy), 'hypoxia', 'chest discomfort', 'dizziness', 'dry throat', 'dyspnea' and 'headache' have been added in section 4.8. Moreover a statement was added in section 6.6 of the SmPC regarding the precautions for disposal of INOmax.
IAIN/0033	A.1 - Administrative change - Change in the name and/or address of the MAH	21/12/2012	16/01/2014	SmPC, Labelling and	

				PL	
IB/0032/G	This was an application for a group of variations. B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	29/11/2012	n/a		
IA/0031	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	24/08/2012	n/a		
N/0029	Inclusion of the list of local representatives at the end of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2012	29/10/2012	PL	
IAIN/0028	C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database	11/05/2012	n/a		
IB/0027	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	10/05/2012	29/10/2012	SmPC	
IB/0026/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	10/05/2012	n/a		

	changes to an approved test procedure 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				
IB/0025	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	06/03/2012	n/a		
X/0021	Annex I_2.(c) Change or addition of a new strength/potency	20/01/2011	18/03/2011	SmPC, Annex II, Labelling and PL	
II/0019	Extension of the therapeutic indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children and adults in 4.1 of the SmPC. Posology instructions for this new indication including attempts for weaning/to wean from INOmax have been proposed in section 4.2. Furthermore, changes to the SmPC have been proposed for section 4.4, 4.8 and 5.1. The PIL has been modified accordingly. Moreover, Annex II was to be updated and an Annex 127a has been introduced. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/01/2011	17/03/2011	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "INOmax/H/C/000337/II/0019" for further information.

II/0022	Update of sections 4.2, 4.4 and 5.1 of the SmPC to include efficacy and safety data from study INOT27, as requested by the CHMP. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	16/12/2010	21/01/2011	SmPC	The safety and efficacy of INOmax in premature infants less than 34 weeks of gestation has not yet been established. In the INOT27 trial, 795 preterm infants (GA<29 weeks) with hypoxic respiratory failure were randomised to receive either INOmax (n=395) in a dose of 5 ppm or nitrogen (placebo n=400), beginning within the first 24 hours of life and treated for at least 7 days, up to 21 days. The primary outcome, of the combined efficacy endpoints of death or BPD at 36 weeks GA, was not significantly different between groups. The overall occurrence of intraventricular haemorrhage was 114 (28.9%) among the iNO treated as compared to 91 (22.9%) among the control neonates. The overall number of death at week 36 was slightly higher in the iNO group; 53/395 (13.4%) as compared to control 42/397 (10.6%). The INOT25 trial, studying the effects of iNO in hypoxic preterm neonates, did not show improvement in alive without BDP. No difference in the incidence of IVH or death was however observed in this study. The BALLR1 study, also evaluating the effects of iNO in preterm neonates, but initiating iNO at 7 days and in a dose of 20 ppm, found a significant increase in neonates alive without BPD at gestational week 36, 121 (45% vs 95 (35.4%) p<0.028. No signs of any increase adverse effects were noted in this study.
IA/0023	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	15/10/2010	n/a	Annex II and PL	

IA/0020	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	01/06/2010	n/a	Annex II and PL	
II/0017	Update of section 5.3 of the SPC following the finalisation of the carcinogenicity study N005243 and the CHMP assessment of Follow Up Measure FU2 013.1. Update of Summary of Product Characteristics	24/09/2009	29/10/2009	SmPC	The SPC has been updated with new statements which are more concise in order to avoid repetition and maintain the non clinical information required by the prescriber. The findings from 2 year carcinogenicity study study showing a low incidence of uterine adenocarcinoma in rats following daily exposure to the recommended human dose have now been included. The wording of the carcinogenicity and mutagenicity information is modified for clarity.
II/0014	Change to the nitric oxide specification: changes in the selection of tests, in the limits, in the analytical methods and in the numbering of the analytical methods Quality changes	24/09/2009	29/09/2009		
IB/0016	IB_33_Minor change in the manufacture of the finished product	03/07/2009	n/a		
IB/0013	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	15/05/2009	n/a		
IA/0015	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	06/05/2009	n/a		
IB/0011	IB_33_Minor change in the manufacture of the finished product	26/02/2009	n/a		

N/0010	The Marketing Authorisation Holder (MAH) applied to update section 6 of the Package Leaflet (PL) to remove the contact telephone and fax numbers of the manufacturer. Additionally, a correction was made in section 6 of the PL for the Latvian translation. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2006	n/a	PL	
R/0008	Renewal of the marketing authorisation.	01/06/2006	28/07/2006	SmPC, Labelling and PL	
IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	03/05/2006	n/a	Annex II and PL	
IA/0007	IA_32_a_Change in batch size of the finished product - up to 10-fold	20/08/2004	n/a		
II/0006	This variation concerns an update of section 4.5 of the Summary of Product Characteristics (SPC) to include prilocaine as an example of a drug with known tendency to increase methaemoglobin, as requested by CHMP following the assessment of the second Periodic Safety Update Report. In addition, section 4.8 of the SPC is updated to reflect data from post-marketing experience. Corresponding changes have been included in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	02/08/2004	SmPC and PL	This variation concerns an update of section 4.5 of the Summary of Product Characteristics (SPC) to include prilocaine as an example of a drug with known tendency to increase methaemoglobin, as requested by the CHMP following the assessment of the second Periodic Safety Update Report (PSUR). In addition the following adverse reactions which had been reported as part of the post-marketing surveillance were added to section 4.8 of the SPC: headaches associated with environmental exposure, hypotension associated with acute withdrawal of the drug, hypoxaemia associated with acute withdrawal of the drug,

					and dose errors associated with the delivery system.
T/0005	Transfer of Marketing Authorisation	08/10/2003	01/12/2003	SmPC, Labelling and PL	Marketing Authorisation transferred from AGA AB to INO Therapeutics AB.
I/0004	01_Change in the name of a manufacturer of the medicinal product	20/08/2003	02/10/2003	Annex II and PL	
I/0003	30_Change in pack size for a medicinal product	23/09/2002	22/10/2002	SmPC, Labelling and PL	
I/0001	31_Change in container shape	21/11/2001	27/02/2002		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2002	02/04/2002	PL	