Intuniv

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/0033/G	This was an application for a group of variations. Submission of the final reports from the Drug Utilisation Study of Intuniv (guanfacine extended release) in European countries: a prescriber survey (EUPAS18739) and a retrospective database study	16/05/2024		Annex II	Deletion of Educational material (including prescriber checklist) for the healthcare professionals from Annex II.

[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).

	(EUPAS18735), listed as category 3 studies in the RMP. The RMP version 4.1 has also been submitted. 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				
IA/0034/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 originally approved batch size 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	08/04/2024	n/a		
IAIN/0032/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 A.1 - Administrative change - Change in the name and/or address of the MAH	03/02/2023	06/02/2024	SmPC, Annex II, Labelling and PL	

IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/10/2022	16/12/2022	SmPC, Annex II and PL	
IA/0030	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/07/2022	n/a		
PSUSA/10413 /202103	Periodic Safety Update EU Single assessment - guanfacine	14/10/2021	20/12/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10413/202103.
IAIN/0028/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.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 A.7 - Administrative change - Deletion of manufacturing sites	09/11/2021	16/12/2022	Annex II and PL	
T/0027	Transfer of Marketing Authorisation	13/08/2021	22/09/2021	SmPC, Labelling and PL	
IA/0025	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	12/04/2021	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IA/0024	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	19/10/2020	n/a		
PSUSA/10413 /202003	Periodic Safety Update EU Single assessment - guanfacine	01/10/2020	n/a		PRAC Recommendation - maintenance
R/0022	Renewal of the marketing authorisation.	30/04/2020	25/06/2020	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Intuniv in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10413 /201903	Periodic Safety Update EU Single assessment - guanfacine	03/10/2019	n/a		PRAC Recommendation - maintenance
IAIN/0021/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 manufacturing site for the FP - Primary packaging site 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	10/09/2019	n/a		

	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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0015	Update of section 4.5 of the SmPC in order to remove the statement on potential drug interactions with drugs that inhibit OCT1 based on final results from study V8953M-SPD503; this is a non-clinical study (Transporter Interaction - OCT1 inhibition). The RMP version 3.0 has also been submitted. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/06/2019	25/06/2020	SmPC	To remove the statement that potential drug interactions with drugs that inhibit OCT1 cannot be excluded from section 4.5 of the SmPC.
IB/0018	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	17/04/2019	n/a		
IB/0016/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of	21/03/2019	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.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.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				
IA/0017/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	08/02/2019	n/a		

PSUSA/10413 /201803	Periodic Safety Update EU Single assessment - guanfacine	04/10/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10413 /201709	Periodic Safety Update EU Single assessment - guanfacine	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0012	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	07/11/2017	n/a		
IAIN/0011	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	16/10/2017	28/09/2018	Annex II and PL	
IAIN/0010/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	16/10/2017	28/09/2018	SmPC, Labelling and PL	
PSUSA/10413 /201703	Periodic Safety Update EU Single assessment - guanfacine	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0008	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/07/2017	n/a		

PSUSA/10413 /201609	Periodic Safety Update EU Single assessment - guanfacine	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10413/201609.
II/0004	Update of sections 4.2 (Posology and Method of Administration), 4.4 (Special Warnings and Precautions for Use), and 4.8 (Undesirable Effects) of the SmPC in order to include a warning and update the safety information as a result of a post-marketing case of hypertensive encephalopathy upon abrupt discontinuation of Intuniv (guanfacine hydrochloride). The Package Leaflet is updated accordingly. Annex II has been updated to include the parameters to be monitored during downward titration: blood pressure and pulse as an additional key element. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. 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, Annex II, Labelling and PL	Assessment of the data provided in the context of this variation led to amendments of the PI to reflect the findings. An additional warning in the SmPC warnings and precautions (Section 4.4) and in the undesirable effects (Section 4.8), with reference to these warnings in section 4.2, regarding hypertensive encephalopathy upon abrupt discontinuation of therapy and that abrupt discontinuation/withdrawal of Intuniv therapy may lead to a greater hypertensive response. The Package Leaflet was updated accordingly. Annex II was also updated to include blood pressure and pulse as additional parameters to be monitored during downward titration.
II/0003/G	This was an application for a group of variations. In compliance with requests in the RMP adopted at the time of MA, the MAH submitted final results of 4 completed non-clinical studies as follows: • Study V7613M-SPD503 (Secondary Pharmacodynamics) • Study V7089M-SPD503 (Drug Interaction)	13/10/2016	16/06/2017	SmPC	Since submission of the non-clinical data to support the initial Market Authorisation Application for Intuniv, new secondary pharmacology and metabolism studies have been conducted to evaluate the pharmacological activity of 3-hydroxy-guanfacine sulfate and to further investigate the potential for CYP inhibition and induction and potential drug interactions. With this variation, data deriving from four completed non-clinical studies were submitted (one

	• Study V7400M-SPD503 and Study V7401M-SPD503 (Metabolism) This group of variations leads to amendments of the Product Information: sections 4.5 and 5.2 of the SmPC were updated to reflect the findings four studies submitted. 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 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				Secondary Pharmacodynamics, one Drug Interaction and two Metabolism studies). Assessment of these studies led to the conclusion that Guanfacine is unlikely to be a substrate BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K at clinically relevant concentrations. Guanfacine is a substrate of the transporters OCT1 and 2. Guanfacine is an inhibitor of MATE1 at clinically relevant systemic concentrations and of OCT1 at clinically relevant portal vein concentrations. Guanfacine is not an inhibitor of MRP2 at clinically relevant intestinal concentrations, but may be an inhibitor of BCRP. Guanfacine is not an inhibitor of OATP1B1 and 1B3 at maximal portal vein concentrations. In addition, guanfacine is not an inhibitor of BCRP, MRP2, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, and MATE2-K at maximal systemic concentrations. Guanfacine is not a direct inhibitor of CYP2B6 and CYP3A at clinically relevant concentrations. In addition, guanfacine is not a time-dependent inhibitor of CYP1A2, 2C9, 2C19, 2D6 or 3A at clinically relevant maximal systemic concentrations. Furthermore, guanfacine is not an in vitro inducer of CYP isozymes via AhR, CAR and PXR at clinically relevant concentrations. Furthermore, in vitro data showed no evidence of agonist or antagonist activity of 3-hydroxy guanfacine sulfate at the human alpha2A, 2B or 2C adrenoceptor. As a result of the above conclusions, sections 4.5 and 5.2 of the SmPC were updated to reflect the findings four studies submitted.
PSUSA/10413	Periodic Safety Update EU Single assessment -	29/09/2016	n/a		PRAC Recommendation - maintenance

/201603	guanfacine				
II/0006	B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	04/08/2016	n/a		
IA/0002	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2015	n/a		
IAIN/0001/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 manufacturing site for the FP - Primary packaging site	16/10/2015	n/a		