Uptravi

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
IB/0044	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	24/04/2024	n/a		
X/0038	Annex I_2.(c) Change or addition of a new strength/potency	25/01/2024	27/03/2024	SmPC, Annex II, Labelling and PL	

[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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IB/0041	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	12/03/2024	n/a		
IB/0040	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)	06/12/2023	27/03/2024	SmPC, Labelling and PL	
II/0039	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	12/10/2023	n/a		
II/0035	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	07/07/2022	n/a		
IB/0037/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	06/07/2022	n/a		

	changes to an approved test procedure				
II/0034	Update of sections 4.8 and 5.1 of the SmPC to add dyspepsia as a new ADR with frequency common, and to include further information on the frequency of dyspepsia and on haemoglobin decrease in patients receiving triple combination therapy, and to add efficacy and mortality data of initial triple combination treatment with selexipag, macitentan and tadalafil in newly diagnosed PAH patients compared to initial double combination treatment with placebo, macitentan and tadalafil, based on the Studies AC-065A308 (TRITON) and AC-065A404 (TRACE). AC-065A308 (TRITON) study was a randomized, double-blind, placebo-controlled, parallel-group, Phase 3b, efficacy and safety study comparing triple oral combination therapy (selexipag, macitentan, tadalafil) with double oral combination therapy (placebo, macitentan, tadalafil) in newly diagnosed, treatment-naïve participants with PAH. The AC-065A404 (TRACE) study was a randomized, double-blind, placebo-controlled, parallel-group, exploratory Phase 4 study in participants with PAH to assess the effect of selexipag on daily life physical activity and participant's self-reported symptoms and their impacts. The package leaflet is updated accordingly. A revised RMP version 9.2 was provided as part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to	19/05/2022	04/07/2023	SmPC and PL	Update of the SmPC section 5.1: In a double blind, placebo-controlled study, a total of 247 newly diagnosed PAH patients were randomised to evaluate the treatment effect of initial triple (selexipag, macitentan and tadalafil) (N = 123) versus initial double (placebo, macitentan and tadalafil) (N = 124) therapy. The primary endpoint, change from baseline in pulmonary vascular resistance (PVR) at Week 26, did not show a statistically significant difference between the groups, while showing an improvement from baseline in both treatment groups (relative reduction by 54% in the initial triple therapy group vs 52% in the initial double therapy group). Over a median follow-up of 2 years, 4 (3.4%) patients in the triple therapy group and 12 (9.4%) patients in the double therapy group died. Section 4.8 of the SmPC was updated to add dyspepsia as a new ADR with frequency 'common' and to include the information that mean absolute changes in haemoglobin at regular visits compared to baseline ranged from - 1.77 to - 1.26 g/dL in the triple therapy group (selexipag, macitentan, tadalafil) compared to - 1.61 to - 1.28 g/dL in the double therapy group (placebo, macitentan and tadalafil). A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 19.0% of patients in the triple therapy group and 14.5% in the double therapy group. Anaemia was reported with very common frequency (13.4%) in the triple therapy group compared to common frequency (8.3%) in the double therapy group. For more information, please refer to the Summary of

	new quality, preclinical, clinical or pharmacovigilance data				Product Characteristics.
IA/0036	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/03/2022	n/a		
PSUSA/10503 /202012	Periodic Safety Update EU Single assessment - selexipag	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	09/03/2021	26/11/2021	SmPC, Annex II 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	17/12/2020	n/a		
R/0030	Renewal of the marketing authorisation.	15/10/2020	14/12/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Uptravi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0029	Update of section 5.1 of the SmPC based on interim survival and safety data from study AC-065A303 a long-term single-arm, open-label study to evaluate the safety and tolerability of selexipag / ACT-293987 in patients with Pulmonary Arterial Hypertension. In addition, the MAH took the opportunity to implement minor editorial changes and update the list of local representatives in the Package Leaflet.	10/12/2020	26/11/2021	SmPC and PL	A sub-set of patients who participated in the pivotal phase 3 trial for the authorisation of selexipag in pulmonary arterial hypertension (PAH), entered a long-term, uncontrolled open-label extension study. Given that additional PAH treatment was initiated in a proportion of those patients and that there was no control group in the extension study, the survival benefit of selexipag cannot be confirmed from these data. The long-term follow up of selexipag treated patients

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				showed a safety profile similar to that which had been observed in the pivotal clinical study. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10503 /201912	Periodic Safety Update EU Single assessment - selexipag	09/07/2020	n/a		PRAC Recommendation - maintenance
IAIN/0027/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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	19/02/2020	14/12/2020	Annex II and PL	
PSUSA/10503 /201906	Periodic Safety Update EU Single assessment - selexipag	16/01/2020	n/a		PRAC Recommendation - maintenance
IA/0026	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)	12/12/2019	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2019	14/12/2020	PL	

II/0022	Update of Sections 4.2, 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study AC-065-117 a listed category 3 study in the RMP which is a clinical pharmacology drug-drug interaction (DDI) study, evaluating the effect of clopidogrel a moderate inhibitor of CYP2C8, on the pharmacokinetics of selexipag and its active metabolite ACT-333679. The package leaflet is updated accordingly. The RMP version 7.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor discrepancies in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	25/07/2019	SmPC, Labelling and PL	When Uptravi is co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of Uptravi to once daily. If the therapy is not tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Revert to twice daily dosing frequency of Uptravi when co-administration of moderate CYP2C8 inhibitor is stopped.
PSUSA/10503 /201812	Periodic Safety Update EU Single assessment - selexipag	11/07/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10503 /201806	Periodic Safety Update EU Single assessment - selexipag	17/01/2019	n/a		PRAC Recommendation - maintenance
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2018	25/07/2019	PL	
T/0019	Transfer of Marketing Authorisation	23/08/2018	28/09/2018	SmPC, Labelling and PL	

PSUSA/10503 /201712	Periodic Safety Update EU Single assessment - selexipag	12/07/2018	n/a		PRAC Recommendation - maintenance
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2018	07/06/2018	Labelling and PL	
IA/0017	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	20/03/2018	n/a		
IA/0015	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	21/02/2018	n/a		
IAIN/0014	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	11/01/2018	n/a		
PSUSA/10503 /201706	Periodic Safety Update EU Single assessment - selexipag	11/01/2018	n/a		PRAC Recommendation - maintenance
IG/0839	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	20/11/2017	07/06/2018	SmPC, Annex II and PL	
II/0010	B.I.a.1.z - Change in the manufacturer of AS or of a	14/09/2017	n/a		

	starting material/reagent/intermediate for AS - Other variation				
IB/0011	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	16/08/2017	n/a		
II/0009	Update of section 4.5 of the SmPC to add information on the effect of selexipag administration on the pharmacokinetics of midazolam, its metabolite 1-hydroxymidazolam and the CYP3A4 metabolism, based on data from the completed clinical pharmacology study AC-065-114, a single-centre, open-label, randomised, two-treatment crossover Phase 1 study investigating the effect of selexipag on the pharmacokinetics of midazolam and its metabolite 1-hydroxymidazolam in healthy male subjects. An updated RMP (version 5.4) has also been submitted, to add the results of study AC-065-114, reclassify 'hyperthyroidism' as an important identified risk and update the PASS timelines and protocol versions in accordance with the current EXPOSURE (PASS AC-065A401, observational cohort study of PAH patients newly treated with either Uptravi (selexipag) or any other PAH specific therapy, in clinical practice) protocol (version 3) and the EDUCATE (PASS AC-065A403, evaluation of risk minimisation measures for medication errors with Uptravi during the titration phase in patients with PAH in clinical practice) protocol version 2. This RMP	06/07/2017	07/06/2018	SmPC	At steady state after up-titration to 1,600 µg selexipag twice a day, no clinically relevant change in exposure to midazolam, a sensitive intestinal and hepatic CYP3A4 substrate, or its metabolite, 1 hydroxymidazolam, was observed. Concomitant administration of selexipag with CYP3A4 substrates does not require dose adjustment.

	version also includes the changes approved within procedure EMEA/H/C/3774/II/007 regarding the results of the DDI study investigating the pharmacokinetic interactions of selexipag with gemfibrozil and rifampicin. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10503 /201612	Periodic Safety Update EU Single assessment - selexipag	06/07/2017	n/a		PRAC Recommendation - maintenance
II/0007	Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to add information on pharmacokinetic interactions with gemfibrozil and rifampicin in healthy subjects, based on the final clinical study report of the completed clinical pharmacology drug-drug interaction study AC-065-113. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update information on the hydrolysis of selexipag based on data from the previously submitted absolute bioavailability study AC-065-110, make minor amendments to sections 5.1 and 5.2 of the SmPC and to bring the PI in line with the latest QRD template version 10. An updated version of the RMP (version 5.3) was also submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to	18/05/2017	29/06/2017	SmPC, Labelling and PL	In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite, the major contributor to efficacy, increased approximately 11-fold. Concomitant administration of Uptravi with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated. The effect of moderate inhibitors of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) on the exposure to selexipag and its active metabolite has not been studied. An adjustment of the dose of Uptravi should be considered in case a moderate inhibitor of CYP2C8 is coadministered or discontinued. A potential pharmacokinetic interaction with moderate inhibitors of CYP2C8 cannot be excluded. In the presence of 600 mg rifampicin, once a day, an inducer of CYP2C8 (and UGT enzymes), the exposure to

	new quality, preclinical, clinical or pharmacovigilance data				selexipag did not change, whereas exposure to the active metabolite was reduced by half. Dose adjustment of selexipag may be required with concomitant administration of inducers of CYP2C8 (e.g., rifampicin, carbamazepine, phenytoin).
IAIN/0006	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	13/01/2017	29/06/2017	SmPC, Labelling and PL	
PSUSA/10503 /201606	Periodic Safety Update EU Single assessment - selexipag	12/01/2017	n/a		PRAC Recommendation - maintenance
IA/0005	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	05/01/2017	n/a		
N/0001	Update of the package leaflet to reflect the approved SmPC contraindication of "Cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last 3 months", and corrections were made to the patient titration guide at the end of the package leaflet. In addition the MAH took the opportunity to make corrections in the Labelling section 5 'Method and Route(s) of Administration' of the Bulgarian, Czech, Danish, Estonian, Slovenian, German and French labelling in line with the English version, and made linguistic amendments in the French, Greek and Swedish labelling, package leaflet and titration guide.	19/09/2016	29/06/2017	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IG/0720	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	16/08/2016	29/06/2017	Annex II and PL	