Opsumit

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/0054	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/10/2024	n/a		
X/0051/G	This was an application for a group of variations.	25/07/2024	19/09/2024	SmPC, Labelling and	Please refer to the Assessment Report Opsumit EMEA-H-C-002697-X-0051-G

[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).

	Extension application to introduce a new pharmaceutical form associated with a new strength (2.5 mg dispersible tablet) grouped with an extension of indication (C.I.6.a) to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years of age of WHO Functional Class (FC) II to III for OPSUMIT. In addition, the indication of the 10 mg coated tablet is extended, as monotherapy or in combination, for the long-term treatment of PAH in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III. This is based on an extrapolation exercise with exposure matching to the adult efficacious dose range given the similarity of the disease in children and adults, as well as on supportive efficacy and safety data from the phase 3 AC-055-312 study (TOMORROW). TOMORROW is a multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC for the film-coated tablets are updated. The Package Leaflet and Labelling are updated in accordance. Version 14.4 of the RMP has also been submitted. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new			PL	

	pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10115 /202310	Periodic Safety Update EU Single assessment - macitentan	13/06/2024	n/a		PRAC Recommendation - maintenance
IB/0052/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.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.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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	21/12/2023	n/a		
IA/0050	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/04/2023	n/a		

IA/0049	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	27/03/2023	n/a		
II/0047	Update of section 4.8 of the SmPC in order to add 'flushing' to the list of adverse drug reactions (ADRs) with frequency 'common' based on a cumulative review of cases (post-marketing, clinical studies, registry) and literature; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/12/2022	29/06/2023	SmPC and PL	
IA/0048	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	25/10/2022	n/a		
II/0046	Update of sections 4.6 and 5.3 of the SmPC in order to introduce additional data on male fertility based on literature search and global safety database. The RMP version 13.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2022	29/06/2023	SmPC	SmPC new text Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men.

II/0043	Update of sections 4.2 and 4.4 of the SmPC to remove a sentence and a warning on the limited clinical experience in patients over the age of 75 years, following the recommendation of the EMEA/H/C/PSUSA/00010115/202010 procedure to remove 'Elderly patients' as missing information in the RMP. The Package Leaflet is being updated accordingly. In addition, the MAH took this opportunity to update the Package Leaflet to include section on Male fertility and align it with the currently approved information in SmPC, sections 4.6 Fertility, pregnancy, and lactation and 5.3 Preclinical safety. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2022	29/06/2023	SmPC and PL	Opus Registry (AC-055-503) is a multicenter, prospective, long-term, longitudinal, real-world, observational drug registry of new users of Opsumit conducted in the US to further characterize the safety profile in clinical practice and to describe clinical outcomes in the postmarketing setting, which included data from 374 patients aged ≥ 75 years (2264 in the PAH set), was submitted supported by an additional data of subgroups by age from previously submitted clinical trials. The effectiveness outcomes in the Opus study were hospitalization and death, and safety outcomes were adverse events (AE), hepatic AE, hepatic AE of special interest and reason for discontinuation. In the elderly subset, 180 patients were hospitalized at least once, and 173 of them were hospitalized due to an AE (dyspnoea, pneumonia, acute respiratory failure, respiratory failure or hypoxia). There were no relevant differences between the elderly subset and the PAH set related to the first hospitalization and death. The KM survival estimates were 82.3% (95% CLs: 77.1, 86.4) at 1 year and 69.3% (95% CLs: 62.3, 75.2) at 2 years (89.5% (95% CLs: 87.9, 90.8) at 1 year and 81.0% (95% CLs: 78.8, 83.0) at 2 years in the PAH set). The exposure-adjusted event rate per 100 persons-years was higher in the elderly subset (17.10 vs 10.19). The rate of death was higher in the elderly subset, which is in line with the higher mortality in this group of patients ≥75 years. No significant differences in the effectiveness and safety profile have been observed in elderly aged 75 and over.
II/0042	Update of the Risk management plan to v12.2 and consequential update of the Annex II and the patient alert card in the labelling based on the outcome of	10/02/2022	05/05/2022	Annex II and Labelling	n/a

	the PRAC assessment of EMEA/H/C/PSUSA/00010115/202010 : - The controlled distribution system and Prescriber Kit (SmPC, prescribing check list and HCP brochure) is being removed as additional risk minimization measures (aRMM) in the RMP and in the product information Annex II.D. Only the patient card is remaining as an aRMM. - Off-label use is being removed from the list of safety concerns. - "Elderly patients aged over 75 years", "Patients with moderate to severe hepatic impairment" and "Patients with severe renal impairment and/ or undergoing dialysis" are being removed as missing information. - The MAH has also taken the opportunity to include in the RMP Annex 4, the updated Specific Follow-up Questionnaires Forms (pregnancies, menstrual disorders, and ovarian cysts) due to revision of internal company template. 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				
II/0044	Update of SmPC sections 4.8 and 5.1, based on the long-term follow-up data from SERAPHIN open-label (OL) study. SERAPHIN OL study was a long-term single-arm open-label extension study of the	13/01/2022	05/05/2022	SmPC	Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label (OL) extension study. The OL cohort included 182 patients who continued on macitentan 10 mg

	SERAPHIN double-blind (DB) study, to assess the safety and tolerability of macitentan in patients with symptomatic pulmonary arterial hypertension (PAH) that have completed the DB study or that experienced a morbidity event and for who a written approval to roll over into the OL study was obtained by the sponsor. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				and 368 patients who received placebo or macitentan 3 mg and crossed over to macitentan 10 mg. Long-term follow-up of these 550 patients for a median exposure of 3.3 years and a maximum exposure of 10.9 years showed a safety profile that was consistent as during the SERAPHIN double-blind phase. In long-term follow-up of 242 patients who were treated with macitentan 10 mg in the double-blind (DB) phase of the SERAPHIN study, 182 of which continued with macitentan in the open-label (OL) extension study (SERAPHIN OL) (DB/OL cohort) , Kaplan-Meier estimates of survival at 1, 2, 5, 7 and 9 years were 95%, 89%, 73%, 63% and 53%, respectively. The median follow-up time was 5.9 years.
IA/0045/G	This was an application for a group of variations. 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 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 A.7 - Administrative change - Deletion of manufacturing sites	06/12/2021	n/a		
PSUSA/10115 /202010	Periodic Safety Update EU Single assessment - macitentan	10/06/2021	n/a		PRAC Recommendation - maintenance

II/0039	Update of sections 4.4, 4.5, and 5.2 of the SmPC in order to add drug-drug interaction information of macitentan with moderate dual inhibitors of CYP3A4 and CYP2C9 based on results from a non-clnical study and a physiologically based pharmacokinetic study in healthy subjects and CYP2C9 poor metabolizers; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to make editorial changes in the labelling. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	05/05/2022	SmPC, Labelling and PL	The cytochrome P450 CYP3A4 is the main enzyme involved in the metabolism of macitentan and in the formation of its active metabolite, with minor contribution from CYP2C8, CYP2C9, and CYP2C19 enzymes. Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone). In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to macitentan may increase approximately 3.8-fold based on PBPK modelling. However, there was no clinically relevant change in exposure to the active metabolite of macitentan. The uncertainties of such modelling should be considered. Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine).
IA/0041/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength	12/03/2021	05/05/2022	SmPC, Annex II, Labelling and PL	

	or pharmaceutical form				
IB/0038/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.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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/06/2020	n/a		
IB/0037	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/06/2020	n/a		
II/0035/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to update the drug-drug interaction information of macitentan with Breast cancer resistance protein (BCRP) substrate drugs based on final results from studies AC-055-122 and AC-055-123 ; these are single-center, open-label, one-sequence, two- treatment studies investigating the effect of macitentan at steady state on the pharmacokinetics of rosuvastatin	17/04/2020	17/02/2021	SmPC	Macitentan 10 mg once daily did not affect the pharmacokinetics of Breast Cancer Resistance Protein (BCRP) substrate drugs (riociguat 1 mg and rosuvastatin 10 mg).

	qnd riociguat respectively in healthy male subjects. In addition, a minor editorial change was introduced in Section 5.1. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet. 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				
IAIN/0036/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	26/02/2020	17/02/2021	Annex II and PL	
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2019	17/02/2021	PL	
PSUSA/10115 /201810	Periodic Safety Update EU Single assessment - macitentan	16/05/2019	n/a		PRAC Recommendation - maintenance

IA/0032	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/11/2018	n/a		
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2018	17/02/2021	PL	
IA/0030	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)	14/11/2018	n/a		
T/0028	Transfer of Marketing Authorisation	23/08/2018	21/09/2018	SmPC, Labelling and PL	
R/0027	Renewal of the marketing authorisation.	28/06/2018	23/08/2018	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Opsumit in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10115 /201710	Periodic Safety Update EU Single assessment - macitentan	17/05/2018	n/a		PRAC Recommendation - maintenance
II/0025/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.II.b.1.c - Replacement or addition of a	18/01/2018	23/08/2018	SmPC, Annex II and PL	

	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.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				
IB/0024	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/07/2017	n/a		
IB/0023/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.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	22/05/2017	n/a		
PSUSA/10115 /201610	Periodic Safety Update EU Single assessment - macitentan	05/05/2017	n/a		PRAC Recommendation - maintenance

IB/0021	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)	10/01/2017	17/07/2017	SmPC, Annex II and Labelling	
IB/0020	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	14/12/2016	n/a		
PSUSA/10115 /201604	Periodic Safety Update EU Single assessment - macitentan	27/10/2016	n/a		PRAC Recommendation - maintenance
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	17/07/2017	Annex II and PL	
PSUSA/10115 /201510	Periodic Safety Update EU Single assessment - macitentan	14/04/2016	n/a		PRAC Recommendation - maintenance
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	13/04/2016	n/a		
IA/0016	A.7 - Administrative change - Deletion of manufacturing sites	23/03/2016	n/a		
IB/0015	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	04/03/2016	15/07/2016	SmPC, Annex II, Labelling	

	(supported by real time data)			and PL	
PSUSA/10115 /201504	Periodic Safety Update EU Single assessment - macitentan	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0007/G	This was an application for a group of variations. Submission of studies AC-055C301/DUAL-1 and AC-055C302/DUAL-2, two completed Phase 3 studies in patients with digital ulcers associated with systemic sclerosis. An updated RMP has been submitted accordingly (latest approved version is v.9.0). 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	24/09/2015	n/a		
IG/0612	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	07/09/2015	15/07/2016	Annex II and PL	
II/0008	Update of section 4.5 of the SmPC in order to update the safety information on drug-drug interaction reporting no interaction between macitentan and hormonal contraceptives. Furthermore the MAH took the occasion to updated section 5.3 of the SmPC to introduce minor correction on two ratios revised	06/08/2015	15/07/2016	SmPC and PL	Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).

	based on data already assessed during Marketing Authorisation Application. In addition the MAH took the opportunity to make some linguistic improvements and correct typographical errors to the Annexes in various languages (BG, CS, DA, DE, EL, ES, ET, FI, FR, HR, HU, IT, LT, LV, MT, PL, PT, RO, SK, SL, SV) and to update administrative information for its local representatives for Estonia, Ireland, Latvia, Lithuania, Malta and United Kingdom. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10115 /201410	Periodic Safety Update EU Single assessment - macitentan	21/05/2015	28/07/2015		Please refer to Opsumit-PSUSA-00010115-201410 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0009	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	23/06/2015	n/a		
PSUV/0003	Periodic Safety Update	20/11/2014	15/01/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0003.
IA/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/09/2014	15/01/2015	SmPC, Labelling and PL	
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/07/2014	n/a		

N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2014	15/01/2015	PL	