Adempas

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/0039	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	25/07/2023	n/a		
II/0037	Extension of indication to add the treatment of PAH in paediatric patients aged less than 18 years of age	26/04/2023	31/05/2023	SmPC and PL	Please refer to Scientific Discussion 'Adempas-H-C-2737-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).

	and body weight ≥ 50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists for ADEMPAS, based on results from pivotal study PATENT-CHILD (Study 15681); this is a Phase III, Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with PAH; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.4 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				37’
IAIN/0038	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	13/02/2023	n/a		
IB/0036/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or	08/08/2022	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
PSUSA/10174 /202109	Periodic Safety Update EU Single assessment - riociguat	05/05/2022	n/a		PRAC Recommendation - maintenance
II/0035	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/04/2022	n/a		
II/0033/G	This was an application for a group of variations. Group of variations: Type II C.I.4. update to SmPC section 4.8 and 5.1 based on the submission of the final clinical study reports of the Phase III long term extension study PATENT-2. Type II C.I.4. update to SmPC section 4.8 and 5.1 based on the submission of the final clinical study	11/11/2021	09/11/2022	SmPC	The Summary of Product Characteristics (SmPC) has been updated with the final data of the long-term extension (LTE) studies, i.e. PATENT 2 (study 12935) and CHEST 2 (study 11349). The LTE studies comprised n=396 and n=237 subjects for PATENT-2 and CHEST-2, respectively. The mean (SD) treatment duration was 1349.9 (750.5) days. Maintenance of clinical efficacy was shown by a persistent increase of 6MWD. The clinical safety profile was similar to that observed during the initial pivotal trials,

	reports of the Phase III long term extension study CHEST-2. The requested group of variations proposed amendments to the Summary of Product Characteristics. 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				including the risk of pulmonary bleeding. The current SmPC already includes a warning on this topic. No new concerns have raised based on the long-term data.
II/0032/G	This was an application for a group of variations. Type II C.I.4. update to SmPC section 4.3 and section 4.5 to contraindicate coadministration of riociguat (adempas) with other sGC stimulators. Type II C.I.4. update to SmPC section 4.5 to rectify the Cmax value related to concomitant use with HAART treatment. The package leaflet is updated accordingly. In addition the MAH takes to opportunity to implement editorial changes and updates to QRD Template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	22/10/2021	SmPC and PL	Section 4.3 and 4.5 of the SmPC has been updated by adding a contraindication for coadministration with other sGC stimulators. SmPC section 4.5 is updated to rectify the riociguat peak plasma concentration (Cmax) increase in combination with HAART treatment.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0031	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/06/2020	n/a		
II/0030	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/03/2020	n/a		
IA/0029	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	03/06/2019	n/a		
PSUSA/10174 /201809	Periodic Safety Update EU Single assessment - riociguat	11/04/2019	n/a		PRAC Recommendation - maintenance
II/0028	Update of sections 4.2, 4.4 and 4.5 of the SmPC to include information for recommended starting dose for riociguat for patients who are on stable doses of strong multi pathway cytochrome P450 proteins (CYP) and P-gp/BCRP inhibitors based on date from Study 17957 which investigated the potential pharmacokinetic (PK) interaction of human immunodeficiency virus (HIV) antiretroviral agents as fixed-dose combination and riociguat in HIV patients, data from a statistical drug-drug interaction (DDI) which was evaluated in study 18634, in which	28/02/2019	17/02/2020	SmPC and PL	Study 17957 investigated the effect of fixed-dose antiretroviral therapies, Atripla, Complera, Stribild, Triumeq, or any approved antiretroviral protease inhibitor in combination with (preferably) Triumeq, on the exposure to riociguat in HIV patients on a stable dose of one of these therapies. Comparison with limited historical data indicated no effect of Atripla on the AUC of riociguat, while HIV combined therapy including ritonavir boosted protease inhibitors, Complera, Stribild and Triumeq increased the exposure by 18, 88, 88 and 159%, respectively. In vitro data showed that the increase is mainly due to inhibition of

	PK data from study 17957 was compared to the historical PK data and data from a nonclinical study to elucidate the DDI potential of the different components included in the HIV combination products in vitro. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				CYP1A1, and partial due to inhibition of CYP3A4. The plasma concentrations in all HIV non-PH patients were in the range of the observed plasma riociguat concentrations in healthy subjects and healthy subjects receiving riociguat on top of ketoconazole. Taking into account the observed safety (albeit after a single dose) and vital signs, it is considered that, with application of the reduced starting dose of 0.5 mg here times a day, prescribers can manage this risk of hypotension caused by riociguat. Sections 4.2, 4.4 and 4.5 of the SmPC have been updated as a consequence. The Package leaflet Labelling has been updated accordingly.
R/0026	Renewal of the marketing authorisation.	15/11/2018	18/01/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Adempas in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10174 /201709	Periodic Safety Update EU Single assessment - riociguat	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0023	Update of section 4.2 of the SmPC in order to add new information regarding posology for transitioning to and from riociguat based on results from study 16719: An open-label, international, multicentre, single-arm, uncontrolled, phase IIIb study of riociguat in patients with pulmonary arterial hypertension (PAH) who demonstrate an insufficient response to treatment with phosphodiesterase-5 inhibitors (PDE-5i). Section 4.5 of the SmPC was updated in parallel to reflect on the main study	25/01/2018	07/03/2018	SmPC and PL	The following recommendations with regards to transitioning between sildenafil or tadalafil and Adempas were made: Patients stopping sildenafil must wait at least 24 hours before taking Adempas. Patients stopping tadalafil must wait at least 48 hours before taking Adempas. Patients stopping Adempas to change to another medicine called a PDE5 inihibitor (e.g. sildenafil or tadalafil) must wait at least 24 hours from their last dose of Adempas before taking the PDE5 inhibitor. Signs and symptoms of hypotension should be monitored after any transition.

	results concerning pharmacodynamic interactions. Minor editorial changes were also implemented throughout the SmPC. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0024/G	This was an application for a group of variations. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/10/2017	07/03/2018	SmPC	
T/0022	Transfer of Marketing Authorisation	07/04/2017	02/05/2017	SmPC, Labelling and PL	
PSUSA/10174 /201609	Periodic Safety Update EU Single assessment - riociguat	06/04/2017	n/a		PRAC Recommendation - maintenance
II/0018/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	30/03/2017	n/a		

	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				
IAIN/0021/G	This was an application for a group of variations. 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 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	14/03/2017	02/05/2017	Annex II and PL	
II/0014	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	23/02/2017	n/a		
II/0019	Update of section 4.5 of the SmPC in order to add information about interactions of riociguat when administered concomitantly with combined oral	26/01/2017	02/05/2017	SmPC, Annex II, Labelling and PL	The CHMP considered that results of an interaction study indicated that ethinyl estradiol and levonorgestrel exposure was not affected when administered on top of a treatment

	contraceptives containing levonorgestrel and ethinyl estradiol to healthy female subjects. Section 4.4 of the SmPC was updated to reinforce the existing messages in sections 4.3 and 4.6 with regards to pregnancy. Furthermore, section 4.5 of the SmPC was updated to correct the list of CYP isoforms involved in the metabolism of riociguat based on in vitro data. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the Product Information in line with the latest QRD template version 10.0 and to update the contact details of the German local representative. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with riociguat. The following text has been added to section 4.5 of the SmPC: "Patients must not get pregnant during Adempas therapy (see section 4.3). Riociguat (2.5 mg three times per day) did not have a clinically meaningful effect on the plasma levels of combined oral contraceptives containing levonorgestrel and ethinyl estradiol when concomitantly administered to healthy female subjects. Based on this study and as riociguat is not an inducer of any of the relevant metabolic enzymes, also no pharmacokinetic interaction is expected with other hormonal contraceptives." Furthermore, the existing messages conveyed in sections 4.3 and 4.6 with regards to pregnancy have been reinforced in section 4.4 of the SmPC as follows: "Pregnancy/contraception Adempas is contraindicated during pregnancy (see section 4.3). Therefore, female patients at potential risk of pregnancy must use an effective method of contraception. Monthly pregnancy tests are recommended."
IB/0017	B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation	11/11/2016	n/a		
IA/0015/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.c - Change in test procedure for AS or starting material/reagent/intermediate - Other	27/10/2016	n/a		

	changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
IA/0016/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	26/10/2016	n/a		

	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/10174 /201603	Periodic Safety Update EU Single assessment - riociguat	29/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0013	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/08/2016	22/08/2016	SmPC and PL	
PSUSA/10174 /201509	Periodic Safety Update EU Single assessment - riociguat	14/04/2016	n/a		PRAC Recommendation - maintenance
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/11/2015	22/08/2016	PL	
PSUSA/10174 /201503	Periodic Safety Update EU Single assessment - riociguat	08/10/2015	n/a		PRAC Recommendation - maintenance
II/0007/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	15/10/2015	SmPC, Labelling and PL	
PSUSA/10174 /201409	Periodic Safety Update EU Single assessment - riociguat	10/04/2015	n/a		PRAC Recommendation - maintenance

II/0006	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
IB/0004	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/12/2014	n/a		
II/0001	Submission of non-clinical study report R-9318, an in vitro study undertaken to determine the M-1 potential to inhibit renal efflux transporters MATE1 and MATE2-K. The study was included as a category 3 study in the RMP, and a revised RMP version 3.0 was provided accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/10/2014	n/a		The applicant provided the requested information regarding the inhibition potential of M-1 towards MATE1 and MATE2-K uptake transporters. Based on the data from these in vitro studies, at clinical relevant concentrations of M-1, no drug-drug interactions due to inhibition of MATEs by M-1 are expected. Therefore, no changes to the product information are necessary. The study was included as a category 3 study in the RMP, and a revised RMP version 3.0 was provided accordingly. The revised RMP version 3.0 is agreed. These study results do not influence the benefit / risk balance of riociguat, which remains unchanged in the authorised indication(s).
IB/0003/G	This was an application for a group of variations. 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 B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	14/10/2014	15/10/2015	SmPC, Labelling and PL	

	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 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 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				
PSUV/0002	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance