Procoralan

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
WS/2569	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	14/12/2023	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).

	authorisation, including the RMP - Other variation				
PSUSA/1799/202304	Periodic Safety Update EU Single assessment - ivabradine	30/11/2023	n/a		PRAC Recommendation - maintenance
IG/1674	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/11/2023	n/a		
IG/1670	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/10/2023	n/a		
IG/1591/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	25/01/2023	n/a		
WS/2050/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.z - Changes (Safety/Efficacy) of Human and	30/09/2021	15/09/2022	SmPC, Annex II, Labelling and PL	

	Veterinary Medicinal Products - Other variation				
PSUSA/1799/202004	Periodic Safety Update EU Single assessment - ivabradine	14/01/2021	n/a		PRAC Recommendation - maintenance
IG/1194	A.7 - Administrative change - Deletion of manufacturing sites	22/01/2020	n/a		
WS/1641	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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)	11/07/2019	n/a		
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/06/2019	15/09/2022	PL	
SW/0050	Post Authorisation Safety Study results - EMEA/H/C-N/PSR/S/0019	18/10/2018	11/01/2019	Annex II	The results of this DUS study showed an increase in adherence to the SmPC guidelines in the post-RMM period compared to the pre-RMM period. This increase in adherence was measured for all the four criteria under study. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted.
PSUSA/1799/201804	Periodic Safety Update EU Single assessment - ivabradine	29/11/2018	n/a		PRAC Recommendation - maintenance

WS/1352/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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)	03/05/2018	n/a		
WS/1180	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the RMP with current information on epidemiology, post-authorisation exposure and post authorisation studies status including the due date of the final study report for Ivabradine Drug Utilisation Study. The Annex II has been updated accordingly. In addition the MAH took the opportunity to align the	11/01/2018	11/01/2019	SmPC, Labelling and PL	

	PI with the latest QRD template 10.0 and introduce minor updates to the ADR terms. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1799/201704	Periodic Safety Update EU Single assessment - ivabradine	30/11/2017	n/a		PRAC Recommendation - maintenance
PSUSA/1799/201604	Periodic Safety Update EU Single assessment - ivabradine	01/12/2016	n/a		PRAC Recommendation - maintenance
WS/0932/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	07/07/2016	n/a		

	specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IAIN/0044	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	06/07/2016	03/04/2017	Annex II	
WS/0914	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 5.1 of the SmPC in order to update the information on retinal safety. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	03/04/2017	SmPC, Annex II, Labelling and PL	In this variation the MAH updated the Product information to indicate that to date there is no evidence of a toxic effect of long-term ivabradine treatment on the retina.
PSUSA/1799/201504	Periodic Safety Update EU Single assessment - ivabradine	06/11/2015	n/a		PRAC Recommendation - maintenance
PSUSA/1799/201410	Periodic Safety Update EU Single assessment - ivabradine	07/05/2015	n/a		PRAC Recommendation - maintenance

IA/0039	A.7 - Administrative change - Deletion of manufacturing sites	30/04/2015	n/a		
IA/0038	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)	20/03/2015	n/a		
II/0034	Update of sections 4.2, 5.1 and 5.2 of the SmPC with the results of a paediatric study in children with dilated cardiomyopathy from 6 months to less the 18 years of age, conducted as part of the Paediatric Investigation Plan of ivabradine in the condition Chronic Heart Failure and submitted in accordance with Article 46 of the Paediatric Regulation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	25/01/2016	SmPC	
II/0030	Update of section 5.1 of the SmPC in order to add information on study CL3-16257-068. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/01/2015	25/01/2016	SmPC	As committed at the time of the initial Marketing Authorisation, the company has provided the report of the clinical study CL3-16257-068, a 6-week randomised double-blind parallel-group international multicentre study to evaluate the anti-anginal efficacy and safety of oral administration of ivabradine compared to placebo on top of a background therapy with a calcium antagonist (amlodipine or nifedipine) in patients with stable angina pectoris. The following information on the study has been included in section 5.1 of the SmPC:

					"In a 1277-patients randomised placebo-controlled study, ivabradine demonstrated a statistically significant additional efficacy on response to treatment (defined as a decrease of at least 3 angina attacks per week and/or an increase in the time to 1 mm ST segment depression of at least 60 s during a treadmill ETT) on top of amlodipine 5 mg o.d. or nifedipine GITS 30 mg o.d. at the trough of drug activity (12 hours after oral ivabradine intake) over a 6-week treatment period (OR = 1.3, 95% CI [1.0–1.7]; p=0.012). Ivabradine did not show additional efficacy on secondary endpoints of ETT parameters at the trough of drug activity while an additional efficacy was shown at peak (3-4 hours after oral ivabradine intake)."
A20/0032	Pursuant to Article 20 of Regulation (EC) No 726/2004, further to the evaluation of data relating to pharmacovigilance, the European Commission requested on 08 May 2014 the opinion of the Agency on whether the marketing authorisations of Corlentor and Procoralan should be maintained, varied, suspended or revoked.	20/11/2014	15/01/2015	SmPC, Annex II and PL	Please refer to the PRAC assessment report: Corlentor/Procoralan EMEA/H/A20/1404
IG/0510	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)	08/12/2014	n/a		
IB/0035/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a	10/11/2014	n/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.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.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
PSUV/0033	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
PSUV/0031	Periodic Safety Update	26/06/2014	22/08/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0031.
II/0029	Update of sections 4.3 and 4.6 of the SmPC in order to extend the current contra-indication during pregnancy and breastfeeding to women of child-bearing potential not using appropriate contraceptive	21/11/2013	18/12/2013	SmPC, Annex II and PL	For further information please refer to the scientific conclusion: Procoralan H-597-II-29-AR.

	measures. In addition, the description of the luminous phenomena (phosphenes) and vision blurred were added to section 4.8 of the SmPC according to information from post-marketing experience and "diplopia" and "visual impairment" were included as undesirable effects in section 4.8 of the SmPC. The changes described above were requested following recommendations from the PRAC Assessment Report for PSUR No 8. The Package leaflet was updated accordingly. Furthermore, the PI was brought in line with the latest QRD template version 9.3. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/07/2013	18/12/2013	PL	
IAIN/0027/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a	13/03/2013	18/12/2013	Annex II and PL	

	manufacturing site for the FP - Primary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0026	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/12/2012	n/a		
II/0023	Update of section 4.4 of the SmPC in order to add a warning that heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which could give rise to severe arrhythmias. In addition another warning was added to section 4.5 of the SmPC that potassium-depleting diuretics should be used with caution in combination with ivabradine due to the risk of severe arrhythmias, especially in patients with long QT interval. In section 4.8 of the SmPC "ECG interval QT prolonged" was added in the SOC "Investigations" under category "uncommon". The Package Leaflet was proposed to be updated in accordance. In addition two numerical mistakes were corrected in section 5.1 of the SmPC. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.0. The requested variation proposed amendments to	20/09/2012	25/10/2012	SmPC, Annex II, Labelling and PL	Since the initial registration, the SmPC of ivabradine states that the use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided since QT prolongation may be exacerbated by heart rate reduction. Physiologically, QT interval varies inversely with heart rate, so an increase in the measured QT interval was predicted under ivabradine as with other heart rate lowering agents. Ivabradine was not shown to cause changes in QT interval other than those resulting from heart rate reduction on uncorrected QT. Nevertheless, in order to reinforce the existing precaution in such high risk population, and further to the extension of indication of ivabradine in congestive heart failure patients, in whom diuretics are widely prescribed in accordance with the current guideline of the European Society of Cardiology, a recommendation was added to use ivabradine with precautions in combination with potassium-depleting diuretics (thiazidic and loop diuretics). The SmPC was also updated with a warning that heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation,

	the SmPC, Annex II, Labelling and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				which may give rise to severe arrhythmias, in particular Torsade de pointes.
IA/0024	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/10/2012	n/a		
IA/0025	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	05/10/2012	n/a		
II/0018	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2011	09/02/2012	SmPC, Annex II and PL	For further information please refer to the scientific conclusion: Procoralan H-597-II-18-AR
IA/0022	A.7 - Administrative change - Deletion of manufacturing sites	21/10/2011	n/a	Annex II and PL	
IA/0021	A.1 - Administrative change - Change in the name and/or address of the MAH	21/10/2011	09/02/2012	SmPC, Labelling and PL	
II/0020	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	26/08/2011	SmPC, Annex II and PL	
IA/0019	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold	10/03/2011	n/a		

	compared to the currently approved batch size				
II/0017	Section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) was updated with information provided by post marketing reports (renewal PSUR covering 25.10.2005 to 25.12.2009) of rash, erythema, pruritis and hypotension, malaise, syncope (possibly linked to bradycardia). The preferred terms in the table in section 4.8 of the SmPC by System Organ Classes were amended according to the MedDRA dictionary version 13.0. Section 4 of the package leaflet was updated accordingly. 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	21/10/2010	29/11/2010	SmPC and PL	
R/0016	Renewal of the marketing authorisation.	24/06/2010	31/08/2010	SmPC, Annex II, Labelling and PL	The CHMP agreed that the renewal can be granted with unlimited validity. The annexes I, II, IIIA and IIIB are updated to bring the product information in line with the latest QRD template.
IA/0015	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/03/2010	n/a		
IB/0014	To change the wording of the indication in section 1 in the Package Leaflet in order to harmonise with the	21/01/2010	n/a	PL	

	approved indication wording in the SmPC. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IA/0013	To change the name of a manufacturing site for primary and secondary packaging of hospital packs only regarding the finished product. IA_05_Change in the name and/or address of a manufacturer of the finished product	21/12/2009	n/a		
II/0010	Following the results of study CL3-16257-057 (CL3-057), the MAH applied for a change to the current indication. The update concerns sections 4.1, 4.3, 4.4, 4.8 and 5.1 of the SPC, the Labelling and the Package Leaflet. The results of a supporting large safety study, Beautiful are also introduced in section 5.1. Furthermore the list of local representatives in the Package Leaflet has been updated for Bulgaria, Cyprus, Latvia, Malta, Sweden and the UK. Extension of Indication	24/09/2009	23/10/2009	SmPC, Labelling and PL	Based on the study results CL3-057 where ivabradine was given as add-on therapy on top of a beta-blockers, the CHMP agreed to amend the indication for the use of ivabradine in combination with beta-blockers in patients inadequately controlled with an optimal betablocker dose and with a heart rate > 60 bpm. Subsequently the sections 4.3, 4.4, 4.8 and 5.1 are amended to reflect the results of the above study. In addition, the results of a safety outcome trial Beautiful, discussed in this application are also introduced. For further information please see the scientific discussion: Procoralan-H-597-II-10-SD.
IB/0012	To tighten the specification limits of the finished product. IB_37_a_Change in the specification of the finished product - tightening of specification limits	21/08/2009	n/a		

II/0011	Update of Summary of Product Characteristics	19/03/2009	05/05/2009	SmPC	Following the 4th PSUR assessment, the CHMP requested an update of Section 4.8 of the SPC to add "ECG prolonged PQ interval".
II/0007	The MAH applied to adjust the acceptance limits of an in-process control test. The proposed change concerns only film-coated tablets containing 5 mg of drug substance. Quality changes	26/06/2008	23/07/2008		
IA/0009	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	23/07/2008	n/a	Annex II and PL	
IA/0008	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	08/05/2008	n/a		
II/0003	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	06/03/2007	SmPC, Annex II, Labelling and PL	Update of the Annexes in compliance with the latest QRD template version 7.2 and to add Bulgarian and Romanian contacts to the List of Representatives in the Package Leaflet.
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	30/11/2006	n/a		
IA/0004	IA_07_a_Replacement/add. of manufacturing site:	30/11/2006	n/a		

	Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms				
IA/0002	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	06/03/2006	n/a		
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	23/02/2006	n/a		