EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ranexa

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
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2021		PL	
IA/0066/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters	27/10/2021	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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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 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 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 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.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 A.7 - Administrative change - Deletion of manufacturing sites 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.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				
PSUSA/2611/ 202101	Periodic Safety Update EU Single assessment - ranolazine	30/09/2021	n/a		PRAC Recommendation - maintenance

IB/0064/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.4.z - Change to in-process tests or limits applied during the manufacture 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.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	02/06/2021	n/a		
II/0063	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/10/2020	26/03/2021	SmPC, Annex II, Labelling and PL	
IA/0062/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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/05/2020	n/a		
IA/0061	A.7 - Administrative change - Deletion of	23/03/2020	26/03/2021	Annex II and	

	manufacturing sites			PL	
IB/0060	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	05/07/2019	n/a		
IA/0059	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	17/05/2019	n/a		
II/0057/G	This was an application for a group of variations. Grouping of 4 type II variations to update sections 4.6 and 5.3 of the SmPC based on the final results from 4 new non-clinical studies (studies TX-259-2004, 2005, 2006 and 2007); study TX-259-2006 is an oral (gavage) study of the effects of ranolazine on fertility and early embryonic development to implantation in rats, study TX-259-2004: An oral (Gavage) study of the effects of ranolazine on embryo/foetal development in rabbits, study TX-259-2005: An oral (Gavage) study of the effects of ranolazine on embryo/foetal development in rats and study TX-259-2007: An oral (Gavage) study of the effects of ranolazine on pre- and post-natal development including maternal function in rats. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement the warning on sodium salt in line with the revised annex to the EC	28/03/2019	10/03/2020	SmPC and PL	The MAH submitted the final results from 4 new non-clinical studies (studies TX-259-2004, 2005, 2006 and 2007). Regarding pregnancy there are limited amount of data from the use of ranolazine in pregnant women. Studies in animals showed embryo toxicity (see Section 5.3). The potential risk for humans is unknown. Ranexa should not be used during pregnancy unless clearly necessary. Regarding breast-feeding, it is unknown whether ranolazine is excreted in human breast milk. Available pharmacodynamic/toxicological data in rats have shown excretion of ranolazine in milk (for details see Section 5.3). A risk to the suckling child cannot be excluded. Ranexa should not be used during breast-feeding. In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6-fold higher than expected in humans, respectively, had no effect on fertility. Embryofetal toxicity studies were conducted in rats and rabbits: no effect were noted in rabbit fetuses when

	guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' in section 2 of the package leaflet, and to update the contact details of the local representatives in Bulgaria, Slovenia and the Slovak republic 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 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				mothers were exposed at levels (AUC) of plasma ranolazine similar to expected human levels. In rats, no effects in fetuses was noted when mothers were exposed to 2-fold greater levels (AUC) than expected in humans, whereas decreased fetal weight and reduced ossification were observed when the exposure of mothers was 7.5-fold than those obtained in humans. Post-natal mortality of pups was not recorded when the exposure of nursing mothers was 1.3 fold higher than in expected humans, whereas at 3-fold higher exposure post-natal mortality was recorded, concomitant with evidence of milk excretion of ranolazine in rats. No adverse effects on newborn rats were observed at levels of exposures similar to those observed in humans.
IAIN/0058/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved	18/03/2019	n/a		

	manufacturer 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)				
IB/0056/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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/12/2018	n/a		
PSUSA/2611/	Periodic Safety Update EU Single assessment -	20/09/2018	22/11/2018		Refer to Scientific conclusions and grounds recommending

201801	ranolazine				the variation to terms of the Marketing Authorisation(s)' for PSUSA/2611/201801.
IB/0055/G	This was an application for a group of variations. 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.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	01/10/2018	n/a		
II/0053	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	12/10/2017	n/a		
IAIN/0052/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 B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product	03/08/2017	20/12/2017	Annex II, Labelling and PL	
II/0051	Update of sections 4.8 and 5.1 of the SmPC in order to reflect the data from the final CSR from study RIVER-PCI; a Phase 3, Randomized, Double-Blind,	15/12/2016	20/12/2017	SmPC, Annex II and PL	In a phase 3, double-blind, placebo-controlled, event-driven trial (RIVER-PCI) in 2604 patients aged ≥18 years with a history of chronic angina and incomplete

	Placebo-Controlled Study of the Effects of Ranolazine on Major Adverse Cardiovascular Events in Subjects with a History of Chronic Angina Who Undergo Percutaneous Coronary Intervention with Incomplete Revascularization. In addition, the MAH took the opportunity to update the details of the local representative in Bulgaria in the Package Leaflet and to bring the Annex II in line with the 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				revascularisation after percutaneous coronary intervention (PCI) patients were up-titrated to 1000 mg twice daily (dosage not approved in the current SmPC). No significant difference occurred in the composite primary endpoint (time to first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation) in the ranolazine group (26.2%) versus the placebo group (28.3%), hazard ratio 0.95, 95% CI 0.82-1.10 p= 0.48. The risk of all cause mortality, CV death or major adverse cardiovascular events (MACE) and heart failure hospitalisation was similar between treatment groups in the overall population; however, MACE were reported more frequently in patients ≥ 75 years treated with ranolazine compared with placebo (17.0% vs 11.3%, respectively); in addition there was a numerical increase in all cause mortality in in patients ≥ 75 years (9.2% vs. 5.1%, p = 0.074). An increased incidence of adverse events was seen among ranolazine treated patients in the RIVER-PCI trial where patients with incomplete revascularization post-PCI were given ranolazine up to 1000 mg twice daily or placebo for approximately 70 weeks. In this study, there was a higher reporting rate for congestive heart failure in the ranolazine group (2.2% vs 1.0% in placebo). Also, transient ischemic attack occurred more frequently in patients treated with ranolazine 1000 mg twice daily compared with placebo (1.0% vs 0.2%, respectively); however, the incidence of stroke was similar between treatment groups (ranolazine 1.7% vs placebo 1.5%).
IB/0050/G	This was an application for a group of variations.	19/02/2016	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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				
PSUSA/2611/ 201501	Periodic Safety Update EU Single assessment - ranolazine	24/09/2015	19/11/2015	SmPC and PL	Please refer to Ranexa PSUSA/00002611/201501 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0048/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.7 - Administrative change - Deletion of manufacturing sites	03/02/2015	n/a		
IB/0046/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.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	08/10/2014	n/a		

	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)				
IAIN/0047/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.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	06/08/2014	08/07/2015	SmPC and PL	
IB/0045/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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 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	10/02/2014	n/a		
PSUV/0043	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	Refer to Scientific conclusions and grounds recommending

					the variation to terms of the Marketing Authorisation(s)' for PSUV/0043.
IA/0044	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	25/10/2013	n/a		
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2013	08/07/2015	PL	
II/0038	Update of section 4.5 of the SmPC in order to include information regarding drug-drug interactions: ranolazine/atorvastatine and ranolazine/metformin. Update of sections: 4.8 of the SmPC to include information on "co-ordination abnormal", "gait disturbance', "dysuria", "urinary retention" and 4.7 of the SmPC to include information on "coordination abnormal" and "diplopia". The above changes were introduced following the recommendations from the AR for PSUR 7. The Package Leaflet was updated accordingly. Furthermore, the PI is being brought in line with the QRD template version 8.3. In addition, the statement regarding Patient Alert Card (PAC) in Annex IIC was updated to reflect the fact that the exact wording of the PAC is presented in Annex IIIA. In addition, the text of the PAC in Annex IIIA was updated to include the reference to statins and tacrolimus interactions, following the recommendations in the AR for Ranexa/II/30. C.I.3.b - Implementation of change(s) requested	25/04/2013	13/11/2013	SmPC, Annex II, Labelling and PL	Section 4.8 of the SmPC was updated with data from clinical studies and from post-marketing experience regarding the following adverse drug reactions (ADRs): 'coordination abnormal', 'gait disturbance', 'paraesthesia', 'diplopia' and 'urinary retention'. In addition, ADRs 'coordination abnormal' and 'diplopia' were added to section 4.7 of the SmPC. These additions do not represent new areas of concerns for this product but are seen as complementary to similar ADRs included already earlier in the SmPC. Also, three in vivo interaction studies were submitted to evaluate the effect of ranolazine on pharmacokinetics of metformin (2 studies) and atorvastatin (1 study). The results of these studies indicated that ranolazine may cause a clinically relevant interaction with metformin (an OCT2 substrate) but not with atorvastatin. The information about these drug-drug interactions (ranolazine/metformin and ranolazine/atorvastatin) was included in section 4.5 of the SmPC.

	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				
IAIN/0041/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.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	03/04/2013	13/11/2013	Annex II and PL	
R/0040	Renewal of the marketing authorisation.	17/01/2013	06/03/2013	Annex II	In the pivotal studies ranolazine has shown to reduce, alone or in combination with other anti-angina drugs, the number of angina attacks and to improve exercise tolerance in patients with chronic angina without clinically significant effects on blood pressure and heart rate. Hypotension is an uncommon ADR and just a few reports of bradycardia have been collected in the post-marketing surveillance. The effects in ethnicities other than Caucasian are still to be evaluated, as for pregnant and lactating women. Ranolazine has a complex pharmacokinetic profile with several sub-groups at risk for increased exposure; CYP3A4

					inhibitors, P-gp inhibitors, CYP2D6 inhibitors, patient with CYP2D6 poor metaboliser status (PM), patients with renal impairment or hepatic impairment. Exposure is also higher in patients in the lower weight range and in the elderly. Careful dose titration is suggested in these sub-groups and a recommendation to reduce the dose in case of poor tolerability has been introduced in the SmPC. Ranolazine can be described to have a narrow therapeutic window. The risk for significant pharmacokinetic interactions is probably greater in the "real world" compared to a clinical trial setting, since ranolazine is likely to be used as a "last chance" drug to presumably more fragile patients treated with multiple drugs and with other concomitant diseases. It is very important that the dosing instruction is precise and correct and takes into account that there are several patient groups that where cautious titration of the dose is needed. Following the assessment of the postmarketing experience with ranolazine from the marketing authorisation the CHMP recommended that the renewal be granted with unlimited validity.
II/0036	Addition of a new manufacturer with two manufacturing site for the production of the drug substance. That is supported by an ASMF. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF	15/11/2012	15/11/2012		

IA/0039	A.7 - Administrative change - Deletion of manufacturing sites	10/10/2012	29/10/2012	Annex II and PL	
IB/0037	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	29/08/2012	n/a		
IB/0035	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	08/06/2012	n/a		
IB/0033	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)	13/04/2012	25/10/2012	SmPC	
II/0030	The MAH proposed the update of section 4.5 of the SmPC in order to add information on interaction with tacrolimus and statins. In addition, sections 4.6 and 5.3 were modified based on the information from previously submitted animal reproduction toxicity studies. Furthermore small modifications were introduced to section 4.8 regarding acute renal failure. Section 4.7 was modified in line with variation II/029. Furthermore, the MAH proposed this opportunity to bring sections 4.1, 4.2, 4.6 and 5.2 of the SmPC in line with the QRD template version 8. Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	16/02/2012	19/03/2012	SmPC and PL	This variation concerns new information on the interactions occurring between ranolazine and statins and ranolazine and tacrolimus, respectively. The revised information on the interaction between ranolazine and statins/ranolazine and tacrolimus has been introduced on the basis of a cumulative review on clinical studies and post-marketing Individual Case Safety Reports. Information that dose adjustments of some statins like simvastatin and lovastatin and CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, tacrolimus, sirolimus, everolimus) may be required as ranolazine may increase plasma concentrations of these drugs.

	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				
IAIN/0034	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	07/03/2012	n/a		
IAIN/0031/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	29/11/2011	n/a		

IA/0032	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	03/11/2011	n/a		
II/0029	Update of Section 4.8 of the SmPC to include confessional state and hallucination under psychiatric disorders. As a consequence Section 4 of the PL was also updated. In addition, EMEA was replaced with EMA in the EMA name/address, telephone number of the local representative in Bulgaria was updated and the version number of the pharmacovigilance system in Annex IIB was deleted. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/04/2011	17/06/2011	SmPC, Annex II and PL	
II/0028	Update of Section 4.8 Undesirable effects following a review of the 4th PSUR. 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	20/01/2011	21/02/2011	SmPC	
II/0026	To introduce an additional manufacturing site for the production of the active substance.	18/11/2010	26/11/2010		

	B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions				
IB/0025/G	This was an application for a group of variations. To add Menarini - Von Heyden GmBH (Leipziger Strasse 7-13, D-01079 Dresden, Germany) as an additional manufactruing site for bulk production of the durg product. To change the bossing of the tablets due to the new manufacturer 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.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	13/07/2010	n/a	SmPC and PL	
II/0023	Update of Summary of Product Characteristics, Annex II, Patient Alert Card and Package Leaflet and Annex IV. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/02/2010	10/05/2010	SmPC, Annex II, Labelling and PL	Following results of an in vivo drug-drug interaction study evaluating the effect of Ranolazine on the pharmacokinetic of metoprolol, the SPC section 4.5 is updated to add that Ranexa 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. Clarification on exposure to other CYP2D6 substrates is also introduced.

					Furthermore, the incidence of arrhythmias in the MERLIN-TIMI 36 study is amended in section 5.1. In addition, quinidine is removed from section 4.5 and patient card to avoid confusion for prescribers, since it is contraindicated in section 4.3. The Patient Alert Card and Package Leaflet are updated accordingly In addition, amendments are introduced by the CHMP in annex II, SmPC and Patient Alert card (PAC) for Ranexa (ranolazine) concerning quinidine. SPC statements in section 4.5 were considered confusing and let prescribers think that a concomitant use of ranolazine and quinidine is possible, whereas the use of quinidine is contra indicated with Ranexa. Therefore, the CHMP considered that quinidine should be removed from the list of P-gp inhibitors in section 4.5 of the SPC. This same contradiction was also present in the Annex II, Patient Alert Card (in labelling). Finally, minor update of the PI are requested for some languages.
IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/01/2010	n/a		
IB/0022	IB_34_b_01_Change in colour/flavour - Increase or addition: colouring system	11/12/2009	n/a	SmPC, Labelling and PL	
IB/0021	IB_33_Minor change in the manufacture of the	15/10/2009	n/a		

	finished product				
II/0020	Update of DDPS (Pharmacovigilance)	23/07/2009	25/08/2009	Annex II	The MAH submitted a revised DDPS. Consequently the version number is amended in Annex II.
II/0019	Update of Summary of Product Characteristics	23/07/2009	25/08/2009	Annex II and Labelling	Annex IIIA is amended by introducing of the patient alert card into Labelling. Consequently, the Annex II has been updated.
II/0018	Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	25/08/2009	SmPC and PL	Further to a request by the EMEA regarding post marketing cases of renal failure in the Eudravigilance database, the CHMP agreed to add the following information regarding acute renal failure in Section 4.8 of the SPC: In this long term study, acute renal failure was also reported with an incidence less than 1% in placebo and ranolazine patients. [...] Post Marketing experience: In post marketing experience, there have been reports of acute renal failure, including in patients with pre-existing mild to moderate renal impairment and/or taking concomitant medications that are known to interact with ranolazine (see sections 4.4 and 4.5). The Package Leaflet is updated accordingly.
IA/0017	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	29/04/2009	n/a	Annex II and PL	
IA/0016	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/04/2009	n/a	Annex II and PL	

IA/0015	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	29/04/2009	n/a	Annex II and PL	
IB/0013	IB_17_a_Change in re-test period of the active substance	16/04/2009	n/a		
IA/0010	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	14/04/2009	n/a		
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	14/04/2009	n/a		
IA/0014	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	06/04/2009	n/a		
IA/0012	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	06/04/2009	n/a		
T/0008	Transfer of Marketing Authorisation	19/12/2008	25/02/2009	SmPC, Labelling and PL	Transfer from CV Therapeutics Europe Limited to Menarini International Operations Luxembourg S.A.
IB/0007	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and	

				PL	
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0004	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0003	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0002	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0001	IB_02_Change in the name of the medicinal product	11/08/2008	n/a	SmPC, Annex II, Labelling and PL	