EMA/398931/2020

Resolor

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
II/0051	Update of the RMP on the patients' exposure based on based on post-marketing reports. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to	25/06/2020		SmPC	The CHMP agreed on the addition of data to the RMP on estimated exposure through the data-lock point of the data review for suicidal ideation and behaviour, including that of the US and on minor editorial changes proposed to the SmPC and RMP. Data provided based on post marketing reports were not

[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).

	new quality, preclinical, clinical or pharmacovigilance data				considered sufficient evidence to support an association of suicidal ideation and behaviour with exposure to prucalopride and to add a new warning in SmPC and package leaflet. A cumulative review of the nonclinical data, clinical data, the global safety database, relevant literature, and external (regulatory) databases through 14 October 2018 concluded that there is insufficient evidence to support an association of suicidal ideation and behaviour with exposure to prucalopride. The introduction of suicidal ideation and behaviour as an important potential risk in the RMP was similarly not considered to be acceptable. Routine pharmacovigilance activities are considered sufficient to detect a signal on this topic. The CHMP concluded that suicidal ideation and behaviour should continue to be closely monitored and any new cases discussed in the next PSUR.
PSUSA/2568/ 201910	Periodic Safety Update EU Single assessment - prucalopride	11/06/2020	n/a		PRAC Recommendation - maintenance
II/0049/G	This was an application for a group of variations. Submission of the final report from study SH555-802 and an independent adjudication on all potential MACE from completed Phase 2/4 clinical studies in adult subjects. This is a non-interventional pharmacoepidemiology safety study with the primary objective to estimate, in real-world settings, the IRR and 95% CI for MACE in initiators of prucalopride compared with initiators of PEG (polyethylene glycol 3350), adjusting for potential confounders. More specifically, the study	27/02/2020	n/a		The results from study SH555-802 did not provide evidence of an increased risk of MACE overall among patients with chronic constipation using prucalopride. In the post hoc analyses, results were also consistent, except for the small subgroup of men older than 55 years of age with an IRR of 2.57 (95% CI, 0.71-9.26). However, as this subgroup had a very small sample size and thus the finding could very well be due to chance. The overall pooled analyses were consistent with the finding of no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG. The number of MACE from the clinical studies in subjects with chronic idiopathic

	aimed to investigate whether the upper bound of the two-sided 95% CI for the adjusted IRR was less than 3.00. The study was designed as a multidatabase study with data from Germany, UK and Sweden with pooled results. German data was later discarded since due to disparate clinical profile of German patients 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				constipation were low, no firm conclusion to exclude the risk of MACE can be reached based on the submitted data, however no new safety information is warranted to be included in the product information. The potential risk of MACE events is closely monitored in PSURs.
II/0046	Please refer to the Recommendations section above. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/02/2019	21/02/2020	SmPC	Migraine and vertigo were added to section 4.8 of the SmPC as uncommon adverse events based on reanalysis of the integrated safety information of 16 double-blind, placebo-controlled studies. Section 4.6 has been updated to emphasize that women of childbearing potential have to use effective contraception during treatment with prucalopride. Resolor is not recommended in women of childbearing potential not using contraception. In the absence of human data in women who breast fed while taking Resolor, a decision should be made whether to discontinue breast feeding or to discontinue Resolor therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
IAIN/0048	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	22/10/2018	31/01/2019	Annex II and PL	

II/0042	Submission of the final clinical study report for the post-authorization drug utilization study SHP555-804 in fulfilment of MEA 006.11, a drug utilisation study to examine characteristics of patients prescribed prucalopride (Resolor) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy outcomes in the UK Clinical Practice Research Database (CPRD). The RMP (v 15.1) has also been updated to reflect the study results. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/09/2018	n/a		
PSUSA/2568/ 201710	Periodic Safety Update EU Single assessment - prucalopride	17/05/2018	n/a		PRAC Recommendation - maintenance
IAIN/0043	A.1 - Administrative change - Change in the name and/or address of the MAH	05/02/2018	31/01/2019	SmPC, Labelling and PL	
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2017	31/01/2019	PL	
PSUSA/2568/ 201610	Periodic Safety Update EU Single assessment - prucalopride	05/05/2017	n/a		PRAC Recommendation - maintenance
PSUSA/2568/ 201510	Periodic Safety Update EU Single assessment - prucalopride	13/05/2016	n/a		PRAC Recommendation - maintenance

N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/12/2015	31/01/2019	PL	
IG/0621	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/10/2015	n/a		
II/0034	Update of the SmPC extending the indication to the male patient population for the treatment of chronic constipation in adults in whom laxatives fail to provide adequate relieve for Resolor. Consequently update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/04/2015	27/05/2015	SmPC and PL	Please refer to the scientific discussion Resolor EMEA/H/C/001012/II/34 for further information.
PSUSA/2568/ 201410	Periodic Safety Update EU Single assessment - prucalopride	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0031	Update of sections 4.2, 5.1, 5.2 and 5.3 of the SmPC in order to reflect the results of Study M0001-C303 conducted in paediatric patients, aged ≥6 months to <18 years and the rat juvenile toxicity study R4488M-SPD555. The Package Leaflet is updated in accordance. Furthermore, the SmPC, Annex II and the PL are updated in line with the latest QRD template version 9.0.	24/07/2014	27/05/2015	SmPC, Annex II and PL	The efficacy and safety of Resolor in paediatric patients (aged 6 months to 18 years) with functional constipation, were evaluated in Study M0001-C303 which consisted of an 8-week double-blind, placebo-controlled trial, followed by a 16 week open-label comparator-controlled (Polyethylene glycol 4000) study of up to 24 weeks. The results of the study showed no difference in efficacy between Resolor and placebo (P= 0.9002). Overall, the safety profile of prucalopride in children was the same as in adults. Based

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				on the results of this study, the CHMP concluded that Resolor should not be used in children and adolescents younger than 18 years. In addition, in a juvenile toxicity study in immature rats, there was evidence of delay to sexual maturation following exposure to high dose levels of prucalopride. Findings of maturation delay had previously been identified in non-clinical studies.
II/0030	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	26/06/2014	n/a		
II/0027	Update sections 4.2 and 5.1 of the Summary of Product Characteristic (SmPC) following provision of the results of the SPD555-401 study, a long-term placebo controlled efficacy/safety study of 6 months duration in patients with chronic constipation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	27/05/2015	SmPC	The efficacy of Resolor beyond three months of treatment has not been demonstrated in placebo-controlled studies. The efficacy and safety of prucalopride in patients (aged ≥18 or older) with chronic constipation, were evaluated in a 24 week multicentre, randomised, double-blind, placebo controlled study (N=364). The proportion of patients with an average weekly frequency of ≥3 Spontaneous Complete Bowel Movements (SCBMs) per week (ie, responders) over the 24-week double-blind treatment phase was not statistically different (p=0.367) between the prucalopride (25.1%) and placebo (20.7%) treatment groups. The difference between treatment groups in the average weekly frequency of ≥3 SCBMs per week was not statistically significant over Weeks 1-12 which is inconsistent with the 3 previous multicentre, randomised, double-blind, 12-week placebo controlled studies demonstrating efficacy at this timepoint in adult patients. The study is therefore

					considered to be inconclusive with respect to efficacy. However, the totality of the data including the previous double-blind placebo controlled 12 week studies support the efficacy of prucalopride. The safety profile of prucalopride in this 24 week study was consistent with that seen in the previous 12 week studies.
R/0032	Renewal of the marketing authorisation.	25/04/2014	06/06/2014	SmPC, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Resolor continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Resolor continues to be favourable in the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
PSUV/0033	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IB/0028/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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	07/02/2014	n/a		

	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				
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2013	n/a		
T/0025	Transfer of Marketing Authorisation from Shire-Movetis N.V to Shire Pharmaceuticals Ireland Limited. Transfer of Marketing Authorisation	04/09/2013	25/09/2013	SmPC, Labelling and PL	
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/08/2013	25/09/2013	PL	
IAIN/0024	A.1 - Administrative change - Change in the name and/or address of the MAH	05/06/2013	25/09/2013	SmPC, Labelling and PL	
IA/0023	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	27/02/2013	25/09/2013	SmPC	
II/0022	Update of section 5.1 of the SmPC in order to add information from the three pivotal trials related to spontaneous bowel movements, specific symptoms associated with constipation, and quality of life. In addition, the MAH took the opportunity to update the list of local representatives and implemented some editorial changes and linguistic corrections in SmPC and Package Leaflet.	13/12/2012	25/09/2013	SmPC, Annex II and PL	Additional efficacy results from the integrated three pivotal studies were summarized for spontaneous bowel movements (SBMs), specific symptoms associated with constipation and quality of life data. Prucalopride's effect on SBM proved to be statistically superior to placebo for the portion of patients that had an increase of ≥1 SBM/week over the 12-week treatment period. Furthermore details from specific symptom subscales of the PAC-SYM on

	Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.2. The requested variation proposed amendments to the SmPC, Annex II, 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				abdominal (bloating, discomfort, pain, and cramps), stool (incomplete bowel movements, false alarm, straining, too hard, and too small), and rectal symptoms (painful bowel movements, burning, and bleeding/tearing), determined at Week 4 and Week 12 and details on the improvement in the Patient Assessment of Constipation-Quality of Life satisfaction subscale (PAC-QOL) were added to Section 5.1 of the SmPC.
IA/0021	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/09/2012	n/a		
IG/0216	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2012	n/a		
IAIN/0019	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	20/06/2012	n/a		
II/0013	Update of sections 4.2., 4.4. and 5.2 of the SmPC in order to update the safety information regarding the use in patients with hepatic impairment . In addition, the MAH took the opportunity to introduce some editorial changes to the SmPC and Package Leaflet. The requested variation proposed amendments to the SmPC and Package Leaflet.	16/02/2012	19/03/2012	SmPC and PL	Study M00001-C103 was an open-label, single dose, parallel group pharmacokinetic study to assess the pharmacokinetics of prucalopride 2mg in patients with impaired hepatic function (moderate (Child Pugh Grade B) and severe (Grade C)) compared with healthy subjects with normal hepatic function. In this small pharmacokinetic study the Cmax and AUC of prucalopride were, on average, 10-20% higher in patients with moderate to severe hepatic impairment compared with healthy subjects. However, the

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				majority of patients included in this study categorised as having severe hepatic impairment had relatively low Child Pugh scores. Therefore it cannot be excluded that severe hepatic impairment significantly influences significantly prucalopride blood levels. The results of this study were included in the SmPC. Furthermore, the CHMP considered that based on the available data the starting dose for patients with severe hepatic impairment should remain 1 mg once daily and that the response should be evaluated before deciding whether to increase the dose.
II/0014	Update of section 5.1 of the SmPC in order to focus the reported efficacy results from the pooled Phase 3 pivotal studies on the approved female-only population. Furthermore, the PI is being brought in line with the latest QRD template version 8.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	23/02/2012	SmPC, Annex II, Labelling and PL	The efficacy results from the pooled Phase 3 pivotal studies (males and females) mentioned in 5.1 of the SmPC were replaced by the efficacy results of these studies on the population targeted in this label (females).
II/0016	Update of section 4.5 of the SmPC in order to update the safety information adding oral contraceptives to the list of drugs with no interaction resulting from a drug interaction study with oral contraceptives (fulfilled FUM 002). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	15/12/2011	30/01/2012	SmPC and PL	Clinical study M0001-C101 demonstrated a lack of effect both during a single dose and steady state administration of prucalopride (at the clinically recommended doses) on the pharmacokinetics and pharmacodynamics of oral contraceptives. Further to these results, oral contraceptives were added to the list of drugs with no interaction with prucalopride.

	clinical, clinical or pharmacovigilance data				
IB/0018	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	03/01/2012	n/a		
IB/0015	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	24/10/2011	n/a	SmPC	- to increase the shelf life of the finished product from 36 to 48 months based on extrapolation of 36 months data in accordance with ICH guideline
IA/0012/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	19/04/2011	n/a		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2011	n/a	PL	Inclusion of the list of local representatives at the end of the package leaflet.
IB/0010	C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	10/03/2011	n/a		Implementation of existing Shire DDPS.
IA/0009	A.1 - Administrative change - Change in the name and/or address of the MAH	19/01/2011	n/a	SmPC, Annex II, Labelling and PL	
IB/0008	C.I.3.a - Implementation of change(s) requested	15/12/2010	n/a	SmPC and PL	Update of section 4.2 and 4.4 to strengthen that Resolor is

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				not recommended for use in men as data for this patient population are currently unavailable as requested by the CHMP following the assessment of the Risk Management Plan version 4.0 (RMP 013) dated 28 September 2010.
IB/0007/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	05/10/2010	n/a	Annex II and PL	
IB/0006	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	05/10/2010	n/a	SmPC	
IA/0005	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	09/09/2010	n/a	Annex II	

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD				
IB/0002/G	This was an application for a group of variations. 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 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 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 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 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 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	30/07/2010	30/07/2010	SmPC, Labelling and PL	

IA/0004	A.1 - Administrative change - Change in the name and/or address of the MAH	08/07/2010	n/a	SmPC, Labelling and PL	
IB/0001	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	05/01/2010	n/a		