

Prandin

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/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2017		Labelling	
WS/0951	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/05/2016	28/04/2017	SmPC	

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).

IG/0649	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	n/a		
PSUSA/2618/ 201412	Periodic Safety Update EU Single assessment - repaglinide	24/09/2015	19/11/2015	SmPC, Annex II and PL	Please refer to NovoNorm-PSUSA/00002618/201412 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IG/0584	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	24/07/2015	n/a		
WS/0658	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update the Product Information to the latest QRD template version 9.0. In addition, minor linguistic and editorial changes have been made in section 4.2 and 4.6 of the SmPC. Finally, linguistic amendments to the following languages have been performed: BG, CS, DA, DE, ES, ET, FI, FR, HR, LT, NO, PL, RO, SK and SV. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/01/2015	19/11/2015	SmPC, Annex II and PL	
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	19/11/2015	PL	
IG/0280	C.I.z - Changes (Safety/Efficacy) of Human and	17/04/2013	n/a		

	Veterinary Medicinal Products - Other variation				
IG/0264	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	04/02/2013	n/a		
IG/0218	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/09/2012	n/a		
WS/0266/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.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	19/07/2012	19/07/2012		
WS/0223	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC in order to include a new drug-drug interaction with deferasirox. Section 2 of the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to delete glycerol from the list of excipients listed in section 3	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	The CHMP introduced updated information on a drug-drug interaction with deferasirox, a weak moderate CYP2C8 inhibitor: "In an interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a weak moderate inhibitor of CYP2C8 and CYP3A4, and repaglinide (single dose, 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) an

	of the carton labelling and to make editorial changes throughout the PI. In addition, the MAH took the opportunity to delete the list of local representatives in the Package Leaflet for Prandin only. Furthermore, the PI is being brought in line with the latest QRD template version 8. C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				increase in Cmax of 62%, and a small, significant decrease in blood glucose values. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4). If repaglinide and deferasirox are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels."
IG/0106/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place 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)	20/10/2011	n/a		
IG/0068	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	11/05/2011	n/a		
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/03/2011	n/a	PL	
IG/0021	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already	12/10/2010	n/a		

	approved manufacturer				
IA/0054	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/01/2009	n/a		
II/0051	Update of sections 4.5 and 4.8 of the Summary of Product Characteristics (SPC) with new safety information regarding the hepatic uptake of repaglinide and the drug-drug interaction between repaglinide and ciclosporin, as requested by the CHMP at the time of the second renewal of the Marketing Authorisation (EMA/H/C/362/R/50). Relevant sections of the Package Leaflet (PL) were updated accordingly. Furthermore, minor corrections have been made in the PL to ensure compliance with the QRD template. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	17/12/2008	SmPC and PL	At the time of the second renewal of the Marketing Authorisation (MA) of Prandin (EMA/H/C/362/R/50), the Marketing Authorisation Holder committed to submit a type II variation to update sections 4.5 and 4.8 of the Summary of Product Characteristics (SPC) with information regarding the hepatic uptake of repaglinide and the drug-drug interaction between repaglinide and ciclosporin (an immunosuppressive drug). Initially, data indicated that repaglinide was metabolised predominately by cytochrome P3A4 (CYP3A4). However, subsequent in vitro studies and clinical studies in healthy volunteers indicate that repaglinide is metabolised predominantly by CYP2C8, and to a lesser extent also by CYP3A4, but that the relative contribution of CYP3A4 can be increased if CYP2C8 is inhibited. Consequently, metabolism, and therefore clearance of repaglinide, may be altered by drugs which influence these CYP-450 enzymes via inhibition or induction. More recent research shows that repaglinide is also a substrate for active hepatic uptake via the organic anion transporting protein OAT1P1B. Furthermore, drugs that inhibit OAT1P1B, alone or concomitantly with inhibition of CYP3A4 and/or CYP2C8, may have a potential to increase plasma concentrations of repaglinide. This information was included in the SPC. ? Based on the above pharmacokinetic findings in connection

					with ciclosporin, known to inhibit OATP1B1 as well as CYP3A4, a statement regarding the effects of ciclosporin on repaglinide pharmacokinetics was included in the SPC. A similar wording regarding the concomitant use of trimethoprim with repaglinide was also included taking into account the larger increase in exposure observed with trimethoprim. Furthermore, information regarding the possible increased risk of hypoglycaemia due to interactions was included in section 4.8 of the SPC.
IB/0053	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/10/2008	n/a		
IA/0052	IA_32_a_Change in batch size of the finished product - up to 10-fold	08/10/2008	n/a		
R/0050	Renewal of the marketing authorisation.	30/05/2008	23/07/2008	SmPC, Labelling and PL	
II/0049	Update of or change(s) to the pharmaceutical documentation	21/02/2008	26/02/2008		
II/0048	Change(s) to the manufacturing process for the active substance	21/02/2008	26/02/2008		
IA/0046	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/11/2007	n/a		
IB/0045	IB_33_Minor change in the manufacture of the finished product	09/08/2007	n/a		

II/0044	Update of sections 4.4, 4.8 and 5.1 of the SPC to reflect the results of an epidemiological Study (cardiovascular outcomes study). Other minor changes have been introduced throughout the product information. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/05/2007	29/06/2007	SmPC, Annex II, Labelling and PL	The MAH undertook an epidemiological study to quantify the potential cardiovascular risk of repaglinide. The purpose of this study was to compare the rate of major cardiovascular events among type 2 diabetic patients treated with repaglinide as monotherapy or as part of combination therapy compared with type 2 diabetic patients, who use sulfonylureas and with other patients who use non-insulin secretagogue metformin or acarbose pharmacotherapy. Based on the study results the SPC was updated to reflect that and that in an epidemiological study, a higher incidence of acute coronary syndrome (e.g. myocardial infarction) was reported in repaglinide treated patients as compared to sulfonylurea treated patients. However, the CHMP acknowledged that causality of the relationship remains uncertain.
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/10/2006	n/a	PL	
IA/0041	IA_09_Deletion of manufacturing site	12/07/2006	n/a		
IA/0039	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	28/10/2005	28/10/2005	SmPC, Labelling and PL	
IB/0037	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	28/06/2005	n/a		
IA/0038	IA_13_a_Change in test proc. for active substance - minor change	09/06/2005	n/a		

II/0036	Update of or change(s) to the pharmaceutical documentation	26/05/2005	01/06/2005		
II/0032	Update of or change(s) to the pharmaceutical documentation	21/04/2005	28/04/2005		
IB/0034	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	30/03/2005	n/a		
IA/0035	IA_13_a_Change in test proc. for active substance - minor change	03/03/2005	n/a		
IB/0033	IB_33_Minor change in the manufacture of the finished product	02/03/2005	n/a		
IB/0031	IB_10_Minor change in the manufacturing process of the active substance IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	02/03/2005	n/a		
II/0027	Update of Summary of Product Characteristics (sections 4.4 and 4.5) and Package Leaflet with recent information on CYP2C8 metabolism and co-administration of trimethoprim and rifampicin. In addition, barbiturates and carbamazepine have been included with the list of substances that reduce the hypoglycaemic effect of repaglinide. Update of Summary of Product Characteristics and Package Leaflet	15/12/2004	04/02/2005	SmPC and PL	Based on recent interaction studies the MAH applied for an update of section 4.4 and 4.5 of the SPC to reflect information on CYP2C8 metabolism and co-administration of trimethoprim and rifampicin. Concerning the interaction between repaglinide and trimethoprim, the CHMP concluded that co-administration of trimethoprim and repaglinide increased the exposure of repaglinide without affecting blood glucose levels in healthy volunteers. Only dosages of 0,25 mg repaglinide and 320 mg trimethoprim (minimal therapeutic dose) have been used in the interaction study. The CHMP was of the opinion

					that, since the safety profile of this combination has not been established with dosages higher than 0.25 mg for repaglinide and 320 mg for trimethoprim, the concomitant use of trimethoprim with repaglinide should be avoided. If necessary, a close clinical and biological monitoring should be recommended. The CHMP concluded that this information should be described in the SPC. Regarding the concomitant use of repaglinide and rifampicin, the CHMP considered that co-administration of rifampicin and repaglinide produces a markedly decreased exposure of repaglinide, especially after end of treatment with rifampicin (effect of induction only). Therefore there is a risk for lack of efficacy. Concomitant use of rifampicin and repaglinide might therefore induce a need for repaglinide dose adjustment which should be based on carefully monitored blood glucose concentrations. The CHMP concluded that this information should be described in the SPC. In addition the barbiturates and carbamazepine have been included with the list of substances that reduce the hypoglycaemic effect of repaglinide in section 4.5 of the SPC. The Package Leaflet has been updated accordingly.
IA/0030	IA_05_Change in the name and/or address of a manufacturer of the finished product	01/02/2005	n/a		
IA/0029	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	17/01/2005	n/a		
IA/0028	IA_47_c_Deletion of a pack size(s)	31/08/2004	n/a	SmPC, Labelling and	

				PL	
IA/0026	IA_09_Deletion of manufacturing site	29/06/2004	n/a		
II/0025	Update of Summary of Product Characteristics	26/02/2004	05/04/2004	SmPC and Annex II	The MAH was requested to update section 4.8 of the SPC following the assessment of the renewal, which included the 7th PSUR for repaglinide. The MAH was requested by CHMP to delete the following text concerning liver disorders in section 4.8 of the SPC: "_however, other causes were implicated in these cases and a causal relationship with repaglinide has not been established." Furthermore, the MAH was requested to bring the SPC in line with the statement in the company core data sheet concerning the need for third party intervention (concerning hypoglycaemia) and to add the term "vasculitis."
IA/0022	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	11/12/2003	n/a		
IA/0024	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2003	n/a		
IA/0023	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2003	n/a		
I/0021	IB_10_Minor change in the manufacturing process of the active substance IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	03/12/2003	n/a		

II/0020	Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	08/10/2003	SmPC and PL	Update following an Urgent Safety Restriction (USR), related to a newly identified interaction between repaglinide and gemfibrozil. A scientific publication demonstrated that gemfibrozil raised the AUC of repaglinide 8.1 fold and prolonged its half-life 3 times. The combination of gemfibrozil and itraconazole resulted in an even more pronounced effect: AUC was raised 19.4-fold, and half-time increased from 1.3 to 6.1h. The MAH in addition searched their safety database and identified five serious and four non-serious reports of hypoglycaemia during treatment with repaglinide and gemfibrozil. Concomitant use was consequently contraindicated and sections 4.3 and 4.5 of the SPC and sections 6 and 7 of the Package Leaflet updated accordingly.
R/0018	Renewal of the marketing authorisation.	22/05/2003	01/08/2003	SmPC, Annex II, Labelling and PL	
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/05/2003	12/06/2003	PL	
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2002	15/01/2003	PL	
I/0017	15_Minor changes in manufacture of the medicinal product	21/11/2002	25/11/2002		
II/0008	Update of Summary of Product Characteristics (section 4.5) and Package Leaflet to reflect new available information on the concomitant use of repaglinide and chlorarithromycin.	30/05/2002	10/09/2002	SmPC and PL	Based on a published study and adverse event reports the MAH applied for an update of section 4.5 of the SPC and section 7 of the Package Leaflet to reflect information regarding the concomitant use of repaglinide and chlorarithromycin. The CHMP concluded that the data showed

	Update of Summary of Product Characteristics and Package Leaflet				that co-administration with clarithromycin, a mechanism based inhibitor of CYP3A4, with repaglinide may result in increased exposure and enhance the bloodglucose-lowering effect of repaglinide. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin increased the repaglinide (AUC) by 40% and Cmax by 67% and increased the mean incremental AUC of serum insulin by 51% and the maximum concentration by 61%. The exact mechanism of this interaction is not clear.
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/05/2002	17/06/2002	PL	
I/0015	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/04/2002	23/04/2002		
I/0014	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	18/04/2002	23/04/2002		
I/0013	24_Change in test procedure of active substance	18/04/2002	23/04/2002		
I/0012	24_Change in test procedure of active substance	18/04/2002	23/04/2002		
I/0011	24_Change in test procedure of active substance	18/04/2002	23/04/2002		
I/0010	24_Change in test procedure of active substance	18/04/2002	23/04/2002		
I/0009	24_Change in test procedure of active substance	18/04/2002	23/04/2002		
I/0004	20_Extension of shelf-life as foreseen at time of authorisation	31/10/2001	28/01/2002	SmPC	

II/0003	- Update of Summary of Product Characteristics (section 4.3, 4.5) and Package Leaflet based on the results of a renal efficacy and safety study - Update of Summary of Product Characteristics (section 4.8) and Package Leaflet regarding information on hepatic dysfunction Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	12/11/2001	SmPC and PL	The MAH submitted an open-label, parallel group, study in which 281 patients with type 2 diabetes and renal impairment were enrolled. Based on the submitted data the CHMP concluded that no special precautions appear to be necessary when using repaglinide in-patients with mild to moderate renal impairment ($\text{CLcr} \geq 40 \text{ ml/min/1.73 m}^2$) and that repaglinide should not be withheld from patients with severe renal insufficiency (CLcr between 20 and $40 \text{ ml/min/1.73 m}^2$) provided that the dose will be carefully titrated. Severe renal insufficiency was consequently deleted from the contraindications, section 4.3 of the SPC. In addition, further to the evaluation of the 2nd Periodic Safety Update Report a comment on the hepatic failure has been added to section 4.8 of the SPC and section 10 of the PL. Following the assessment of the fourth PSUR the CHMP requested the MAH to update section 4.5 and 4.8 of the SPC to include information on interaction with other antidiabetic agents. The following information was added to section 4.8 of the SPC: "During post marketing experience, cases of hypoglycaemia have been reported in patients treated in combination with metformin or thiazolidinedione".
I/0005	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	26/10/2001	05/11/2001		
I/0002	08_Change in the qualitative composition of immediate packaging material	06/06/2001	16/07/2001		

I/0001	20_Extension of shelf-life as foreseen at time of authorisation	06/06/2001	n/a	SmPC, Labelling and PL	
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