NovoNorm

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/0090	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).

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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 perfomed: 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/0084	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.I.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		
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 approved manufacturer	12/10/2010	n/a		

IA/0077	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/01/2009	n/a		
II/0074	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 (EMEA/H/C/187/R/73). Relevant sections of the Package Leaflet (PL) were updated accordingly. Furthermore, minor corrections have been made in the PL to ensure compliance with the latest 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 Novonorm (EMEA/H/C/187/R/73), 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/0075	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/10/2008	n/a		
IA/0076	IA_32_a_Change in batch size of the finished product - up to 10-fold	08/10/2008	n/a		
R/0073	Renewal of the marketing authorisation.	30/05/2008	23/07/2008	SmPC, Labelling and PL	
II/0072	Update of or change(s) to the pharmaceutical documentation	21/02/2008	26/02/2008		
II/0071	Change(s) to the manufacturing process for the active substance	21/02/2008	26/02/2008		
IA/0070	IA_05_Change in the name and/or address of a manufacturer of the finished product	05/11/2007	n/a		
IB/0069	IB_33_Minor change in the manufacture of the finished product	09/08/2007	n/a		

II/0068	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.
IA/0067	IA_09_Deletion of manufacturing site	12/07/2006	n/a		
IA/0066	IA_09_Deletion of manufacturing site	12/07/2006	n/a		
IA/0064	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/0062	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	28/06/2005	n/a		
IA/0063	IA_13_a_Change in test proc. for active substance - minor change	09/06/2005	n/a		

II/0061	Update of or change(s) to the pharmaceutical documentation	26/05/2005	01/06/2005		
II/0057	Update of or change(s) to the pharmaceutical documentation	21/04/2005	12/05/2005		
IB/0059	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	30/03/2005	n/a		
IA/0060	IA_13_a_Change in test proc. for active substance - minor change	03/03/2005	n/a		
IB/0058	IB_33_Minor change in the manufacture of the finished product	02/03/2005	n/a		
IB/0056	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/0052	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	02/02/2005	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/0055	IA_05_Change in the name and/or address of a manufacturer of the finished product	01/02/2005	n/a		
IA/0054	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	17/01/2005	n/a		
IA/0053	IA_47_c_Deletion of a pack size(s)	31/08/2004	n/a	SmPC, Labelling and PL	

IA/0051	IA_09_Deletion of manufacturing site	29/06/2004	n/a		
II/0050	The Marketing Authorisation Holder applied to update section 4.8 of the Summary of Product Characteristics (SPC) as requested by the CPMP following the renewal of NovoNorm. The changes concern the deletion of a sentence regarding liver disorders and the causal relationship with repaglinide, the inclusion of a wording regarding third party assistance in case of severe hypoglycaemia and the inclusion of a wording regarding vasculitis in section 4.8 of the SPC. In addition the MAH applied to implement minor linguistic improvements in the SPC and took the opportunity to make a correction in the Annex II. Update of Summary of Product Characteristics	26/02/2004	31/03/2004	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/0047	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	11/12/2003	n/a		
IA/0049	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2003	n/a		
IA/0048	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/0046	IB_10_Minor change in the manufacturing process of the active substance IB_12_b_02_Change in spec. of active subst./agent	03/12/2003	n/a		

	in manuf. of active subst. - test parameter				
II/0045	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/0044	Renewal of the marketing authorisation.	22/05/2003	01/08/2003	SmPC, Annex II, Labelling and PL	
I/0043	15_Minor changes in manufacture of the medicinal product	21/11/2002	26/11/2002		
II/0035	Update of Summary of Product Characteristics (section 4.5) and Package Leaflet to reflect new available information on the concomitant use of repaglinide and clarithromycin. Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	09/09/2002	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 chlarithromycin. The CHMP concluded that the data showed 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.
I/0042	01_Change in the name of a manufacturer of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/04/2002	30/04/2002		
I/0041	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	18/04/2002	30/04/2002		
I/0040	24_Change in test procedure of active substance	18/04/2002	30/04/2002		
I/0039	24_Change in test procedure of active substance	18/04/2002	30/04/2002		
I/0038	24_Change in test procedure of active substance	18/04/2002	30/04/2002		
I/0037	24_Change in test procedure of active substance	18/04/2002	30/04/2002		
I/0036	24_Change in test procedure of active substance	18/04/2002	30/04/2002		
I/0032	20_Extension of shelf-life as foreseen at time of authorisation	31/10/2001	28/01/2002	SmPC	
I/0033	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	26/10/2001	05/11/2001		

II/0031	Update of Summary of Product Characteristics (sections 4.5 and 4.8) to include information on hypoglycaemia following the use of repaglinide with other antidiabetic agents. Update of Summary of Product Characteristics	31/05/2001	17/09/2001	SmPC	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".
II/0026	- Update of Summary of Product Characteristics (section 4.3) 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 with regards to information on hepatic dysfunction. Update of Summary of Product Characteristics and Package Leaflet	16/11/2000	05/03/2001	SmPC and PL	
I/0025	25_Change in test procedures of the medicinal product	26/04/2000	04/05/2000		
I/0024	25_Change in test procedures of the medicinal product	26/04/2000	04/05/2000		
I/0023	17_Change in specification of the medicinal product	26/04/2000	04/05/2000		
II/0022	Change(s) to the manufacturing process for the active substance	19/01/2000	22/02/2000		
II/0016	Update of Summary of Product Characteristics and Package Leaflet	23/09/1999	20/01/2000	SmPC and PL	

I/0020	20_Extension of shelf-life as foreseen at time of authorisation	20/10/1999	13/12/1999	SmPC	
I/0021	21_Change in shelf-life after first opening	20/10/1999	04/11/1999		
I/0019	24_Change in test procedure of active substance	20/10/1999	04/11/1999		
I/0018	15a_Change in IPCs applied during the manufacture of the product	20/10/1999	04/11/1999		
I/0017	20a_Extension of shelf-life or retest period of the active substance	20/10/1999	04/11/1999		
I/0014	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	08/02/1999	n/a		
I/0013	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	08/02/1999	n/a		
I/0012	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	08/02/1999	n/a		
I/0011	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	08/02/1999	n/a		
I/0010	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	08/02/1999	n/a		

I/0009	12_Minor change of manufacturing process of the active substance	23/09/1998	01/10/1998		
I/0008	12_Minor change of manufacturing process of the active substance	23/09/1998	01/10/1998		
I/0007	12_Minor change of manufacturing process of the active substance	23/09/1998	01/10/1998		
I/0006	12_Minor change of manufacturing process of the active substance	23/09/1998	01/10/1998		
I/0005	12_Minor change of manufacturing process of the active substance	23/09/1998	01/10/1998		
I/0004	20a_Extension of shelf-life or retest period of the active substance	23/09/1998	01/10/1998		
I/0003	16_Change in the batch size of finished product	23/09/1998	01/10/1998		
I/0002	08_Change in the qualitative composition of immediate packaging material	23/09/1998	01/10/1998		
I/0001	08_Change in the qualitative composition of immediate packaging material	23/09/1998	01/10/1998		