Starlix

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
IB/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/11/2021		SmPC, Annex II, Labelling and PL	
PSUSA/2128/ 202006	Periodic Safety Update EU Single assessment - nateglinide	11/02/2021	n/a		PRAC Recommendation - maintenance

[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

IA/0039	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	15/12/2020	n/a		
IA/0038	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	15/12/2020	n/a		
II/0036/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	19/03/2020	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.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.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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 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.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a				

	test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0035/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	05/09/2018	n/a		

	procedure B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
T/0034	Transfer of Marketing Authorisation	06/04/2018	08/05/2018	SmPC, Labelling and PL	
II/0033	Update of sections 4.4 and 5.2 of the SmPC to add information on the accumulation of M1 metabolite in diabetic patients with end-stage renal disease (ESRD), based on the review of the Core Data Sheet. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with QRD template v. 10, combine the SmPC into a single SmPC, align sections 1 and 2 of the package leaflet with the SmPC, and correct the name of the local representatives for Latvia and Bulgaria. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	11/04/2019	SmPC, Annex II, Labelling and PL	The SmPC sections 4.4 and 5.2 have been updated as follows: Section 4.4 "Special warnings and precautions for use" "Patients with severe renal impairment (see section 5.2) who have not undergone haemodialysis are more susceptible to the glucose-lowering effect of Starlix. Discontinuation should be considered in patients with severe renal impairment who present with potentiation of the hypoglycaemic effect. Section 5.2 "pharmacokinetic properties"; .Although M1 metabolites show only slight hypoglycaemic activity (approximately 5 times lower than nateglinide), metabolite accumulation might increase the hypoglycaemic effect of the administered dose. Therefore, dose discontinuation is advisable in patients with severe renal

					impairment who present with potentiation of hypoglycaemic effect while on Starlix. The PL has been updated accordingly.
PSUSA/2128/ 201706	Periodic Safety Update EU Single assessment - nateglinide	08/02/2018	n/a		PRAC Recommendation - maintenance
IA/0031/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.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	28/11/2016	n/a		
IB/0030	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/06/2015	10/12/2015	SmPC, Annex II, Labelling and PL	
PSUV/0028	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IAIN/0029	A.1 - Administrative change - Change in the name and/or address of the MAH	19/12/2014	10/12/2015	SmPC, Labelling and PL	
IA/0027/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	28/01/2014	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2013	10/12/2015	PL	
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IB/0024/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/12/2012	n/a		
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	27/01/2012	n/a		
II/0021	Update of the SPC and PL based on the revised Core Data Sheet. Additionally, the PL is updated in order to reflect the results of a PL readability testing. And finally, the MAH took the opportunity to implement the latest QRD template in the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC, Annex II, Labelling and PL	In this variation, the MAH has submitted a detailed assessment on drug interaction and clinical pharmacology sections including pharmacodynamics and pharmacokinetics. Based on the provided data on interactions, the product information has been updated to include the additional following agents that may enhance the hypoglycaemic effect of nateglinide: non-steroidal anti-inflammatory agents, salicylates, monoamine oxidase inhibitors, non-selective

					beta-adrenergic-blocking agents and anabolic hormones (eg. methandrostenolone). Additionally, the product information has been updated with the following additional agents that may reduce the hypoglycaemic effect of nateglinide: somatropin, somatostatin analogues (eg. lanreotide, octreotide), rifampin, phenytoin and St John's wort.
II/0022	Update of section 5.3 of the SmPC to include non clinical safety data following an update of the MAH's Core Data Sheet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC	The purpose of the current submission is to update section 5.3 of the SmPC ('Preclinical safety data') following a Novartis Core Data Sheet update. No new relevant non-clinical data have been provided by the MAH. In reproductive and developmental toxicity studies, there was no relevant effect of nateglinide on fertility, embryofoetal development, parturition, lactation, and perinatal development in rats. In rabbits, nateglinide was embryotoxic with increased early intrauterine deaths and the incidence of gallbladder agenesis and hypoplasia was increased at doses of 300mg/kg/day and above. The pre-clinical safety data section of the SmPC was updated accordingly. Nateglinide is contra-indicated during pregnancy and breastfeeding and the updated information does not alter the benefit - risk assessment.
IA/0020	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/07/2008	n/a		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2007	n/a	PL	

N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/07/2007	n/a	PL	
II/0017	This variation refers to an update of section 4.8 of the Summary of Product Characteristics concerning gastro-intestinal events associated with nateglinide following a request from the CHMP to reflect the findings from a six month observational safety study in patients treated with nateglinide or gliclazide in combination with metformin. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	01/06/2006	13/07/2006	SmPC and PL	Study DJN608AGB05 was a 6-months multi center, prospective, observational non interventional and non blinded study in subjects treated with either nateglinide or gliclazide in combination with metformin. A statistically significant difference in the frequency of gastrointestinal disorders was reported between the total nateglinide and total gliclazide groups (5.6 vs. 0.4%! ; p<0.001). This was the only System Organ Class (SOC) for which a significant difference was observed between treatment groups. The SPC has been updated to reflect these findings and therefore abdominal pain, diarrhoea, dyspepsia, nausea and vomiting have been included as an adverse reaction in section 4.8 of the SPC. Section 4 of the Package Leaflet has been updated accordingly.
R/0016	Renewal of the marketing authorisation.	23/02/2006	24/04/2006	SmPC, Annex II, Labelling and PL	
II/0015	The Marketing Authorisation Holder (MAH) applied for this variation to update section 5.1 of the Summary of product Characteristics (SPC) to reflect information from a study comparing the efficacy of nateglinide plus metformin versus a sulphonylurea plus metformin, as requested by the CHMP. In addition, the MAH applied for a combined labelling text, combining the different pack-sizes of the same	27/07/2005	05/09/2005	SmPC, Labelling and PL	The efficacy of nateglinide in combination with metformin has been compared to the combination of gliclazide plus metformin in a 6-month randomised, double-blind trial in 262 patients using a superiority design. The decrease from baseline in HbA1C was −0.41% in the nateglinide plus metformin group and -0.57% in the gliclazide plus metformin group (difference 0.17%, 95% CI -0.03, 0.36). Both treatments were well-tolerated.

	strength in accordance to the QRD template. The MAH also applied to include minor linguistic changes in different language versions of the Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet				Section 5.1 of the SPC has been updated to reflect this information.
IA/0014	IA_05_Change in the name and/or address of a manufacturer of the finished product	11/11/2004	n/a		
II/0012	Update of the SPC and PL following the assessment of the 5th Periodic Safety Update Report. Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	02/08/2004	SmPC, Annex II and PL	As a response to the CHMP conclusions of the 5th Periodic Safety Update Report covering the period 1 January 2003 to 30 June 2003, the Marketing Authorisation Holder applied to add a warning to section 4.4 of the SPC for the risk of hypoglycaemia in patients with severe renal impairment. A recommendation has also been added to section 4.2 of the SPC for a starting dose at 60 mg three times daily in patients who are close to their therapeutic target, assessed by HbA1c levels. Consequential changes have been made to the Package Leaflet.
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
IB/0011	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	28/04/2004	n/a		
IB/0010	IB_10_Minor change in the manufacturing process of the active substance	01/04/2004	n/a		
II/0009	Update of the Summary of Product Characteristics (SPC) to include new information regarding the	25/09/2003	14/01/2004	SmPC and PL	

	interaction between nateglinide and sulfinpyrazone and to include information on the co administration of nateglinide and gemfibrozil. The Package Leaflet has been updated accordingly. The paragraph on hepato-biliary disorders in section 4.8 of the SPC has been updated. In addition minor changes and an update of the local representatives have been done. Update of Summary of Product Characteristics and Package Leaflet				
I/0008	17_Change in specification of the medicinal product	10/10/2002	n/a		
I/0007	20_Extension of shelf-life as foreseen at time of authorisation	17/07/2002	30/08/2002	SmPC	
I/0003	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	12/06/2002	11/07/2002	Annex II and PL	
I/0004	16_Change in the batch size of finished product	12/06/2002	20/06/2002		
I/0006	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	24/05/2002	29/05/2002		
I/0005	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	24/05/2002	29/05/2002		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2001	27/03/2002	PL	

I/0001	04_Replacement of an excipient with a comparable excipient	08/06/2001	n/a		