CONTROLOC Control

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
IG/1503	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	16/05/2022	n/a		
WS/2154	This was an application for a variation following a worksharing procedure according to Article 20 of	22/04/2022		SmPC, Labelling and	Pantoprazole has been reported to be associated with presumably hypersensitivity caused acute interstitial

[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).

	Commission Regulation (EC) No 1234/2008. C.1.4 - Update section 4.8 of the SmPC to update the existing term "Interstitial nephritis" to "Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)", frequency "not known" in line with the updated Company Core Data Sheet. In addition, section 4.4 of the SmPC for centralised authorised products is updated with the Excipient warning for Sodium as per EMA guideline EMA/CHMP/302620/2017/EN Rev. 1. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL and to bring the PI in line with the last QRD template (version 10.1). This procedure also includes NAPs as listed in Annex B. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			PL	nephritis. It is known for many years already that PPIs are associated to hypersensitivity caused acute interstitial nephritis (Muriithi et al, 2014). Whilst in retrospective studies also more protracted nephrotoxicity, where mixed inflammatory cell interstitial infiltrate involving tubulitis (Torpey et al, 2004, Geevasinga et al., 2006, Moledina and Perazella, 2016, Samal et al., 2020) was shown, current evidence is based on retrospective studies in which the observed toxicity was confounded by patient's underlying conditions such as diabetes mellitus or low haemoglobin level. For more information, please refer to the Summary of Product Characteristics.
WS/1891/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. 1. To update section 4.8 of the SmPC adding Hypokalaemia to the list of adverse drug reactions of Takeda's Pantoprazole containing drugs including a	14/01/2021		SmPC, Annex II, Labelling and PL	1. Hypomagnesemia is a rare, potentially serious, adverse class effect of PPIs. It is typically accompanied by hypocalcaemia, hypokalaemia and functional hypoparathyroidism. Of the 97 cases of hypocalcaemia reported, 85 cases (87%) also included the event of hypomagnesemia. The remaining 12 cases which did not report hypomagnesemia as an additional event were confounded by the patient's medical history and/or other

	food note in 4.8 that hypokalaemia may be related to the occurrence of hypomagnesaemia based on a review of the global safety database for cases containing the PT "hypocalcaemia" in patients who were treated with Takeda PPIs (Dexlansoprazole, Lansoprazole and Pantoprazole). The existing warning regarding Hypomagnesaemia in Section 4.4. is proposed to be adapted accordingly. adding also that Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia and that hypomagnesaemia associated hypocalcaemia and/or hypokalaemia improved after magnesium replacement and discontinuation of the PPI. The Package Leaflet is updated accordingly. 2. To update section 4.8 of the SmPC in order to add DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) with the frequency "unknown" based on a comprehensive review of the global safety database for all cases containing the PT "Drug reaction with eosinophilia and systemic symptoms" on all PPIs that are currently marketed by Takeda (i.e. lansoprazole, pantoprazole sodium, pantoprazole magnesium and dexlansoprazole). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the last QRD template (version 10.1), to update the list of local representatives and to implement editorial corrections to the PI. The requested grouped work-sharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.				concomitant medications. 32 cases out of 97 cases (33%) contained the event of hypokalaemia as well as hypocalcaemia and hypomagnesemia. Recovery on cessation of PPI use and recurrence of the event upon re-challenge, strengthened the causal association. 2. 69 (72 events) cases of DRESS were identified with patients on pantoprazole. The cases reported with pantoprazole amounted to 69% of cases of DRESS identified with Takeda PPIs. 67 (97%) of those cases were classified as serious, 2 (3%) were considered non-serious. There were no cases of positive rechallenge for pantoprazole. However, re-challenge tests to ascertain the link between DRESS and any drug is particularly problematic, as reintroduction of the culprit drug in patients may result in fatality. This would explain why so few cases of re-challenge for this PT have been recorded. A postulated mechanism in the literature such as hapten, prohapten, and the p– i concept may play roles in the pathogenesis of these reactions. 48% of reported DRESS events appeared within 2 to 6 weeks following treatment with pantoprazole (and/or lansoprazole), which is consistent with the recognized pathophysiology of the disease. Pantoprazole have a significant number of reports for DRESS. DRESS is an established important identified risk documented umbrella term of SCAR in the pantoprazole RMP. For more information, please refer to the Summary of Product Characteristics.

	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				
IG/1302	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	20/11/2020	n/a		
IG/1155/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	18/11/2019	n/a		
IG/1120	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2019	04/02/2020	SmPC and PL	
IG/1047/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	04/03/2019	n/a		

	relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
WS/1422	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	17/01/2019	04/02/2020	SmPC	
IG/1010	A.7 - Administrative change - Deletion of manufacturing sites	12/12/2018	n/a		
IG/0964/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or	26/07/2018	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
PSUSA/2285/201708	Periodic Safety Update EU Single assessment - pantoprazole	26/04/2018	02/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2285/201708.
IG/0924	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/04/2018	n/a		
IG/0880	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	11/12/2017	n/a		
IG/0864	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	07/12/2017	n/a		
WS/1041	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	28/04/2017	SmPC and PL	
IG/0742	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2016	28/04/2017	SmPC and PL	

IG/0657	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	25/01/2016	n/a		
IG/0634	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/11/2015	08/12/2016	SmPC and PL	
IG/0586/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer A.7 - Administrative change - Deletion of manufacturing sites B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	08/07/2015	n/a		
T/0020	Transfer of Marketing Authorisation	11/06/2015	08/07/2015		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/02/2015	08/07/2015	PL	

IG/0425	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	24/03/2014	n/a		
IG/0416/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 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 B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	24/03/2014	n/a		

	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer 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				
R/0016	Renewal of the marketing authorisation.	19/12/2013	21/02/2014	SmPC 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 non-prescription Pantoprazole continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of non-prescription Pantoprazole continues to be favourable in the treatment of short-term reflux symptoms (e.g. heartburn, acid regurgitation) in adults. The CHMP was of the opinion that

					the renewal could be granted with unlimited validity.
WS/0341	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The Worksharing Applicant (WSA) proposed the update of section 4.5 of the SmPC in order to add an interaction between pantoprazole and methotrexate following the assessment of cases of interaction and published literature in FUMs 13, 12, 12, 18, 13. The Package Leaflet was updated accordingly. Furthermore, the WSA used this opportunity to bring the PI in line with the latest QRD template version 9. 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	25/04/2013	30/05/2013	SmPC, Annex II, Labelling and PL	In a cumulative review of cases of interaction between pantoprazole and methotrexate, including published literature it was shown that concomitant use of PPIs with methotrexate may elevate and prolong serum levels of methotrexate possibly leading to methotrexate toxicities. Current evidence supporting reduced methotrexate elimination in patients receiving PPIs is primarily based on studies conducted in patients receiving high dose treatment, which is usually carried out in a specialist medical setting. Nevertheless, considering the evidence available to date a mention of these facts was added to 4.5 of the SmPC of OTC pantoprazole.
IG/0284	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/03/2013	n/a		
IG/0268/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	08/02/2013	30/05/2013	SmPC, Annex II, Labelling and PL	

	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) 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)				
IG/0255/G	This was an application for a group of variations. 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 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	12/12/2012	n/a		
IG/0212	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2012	n/a		
IG/0157/G	This was an application for a group of variations. B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur.	09/03/2012	n/a		

	Monograph - New certificate from an already approved manufacturer				
IG/0134/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	09/12/2011	n/a		
WS/0122	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 4.8 of the SPC to add Agranulocytosis, Pancytopenia, Hypomagnesaemia, Taste disorders and Gynaecomastia as new adverse drug reactions based on post-marketing data and literature references. Section 4 of the PL is updated accordingly. Furthermore the MAH took the opportunity to bring the Product Information in line with QRD template vs. 7.3.1. and to update the list of local representatives. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	20/10/2011	05/12/2011	SmPC and PL	Following post marketing surveillance data section 4.8. of the SPC was updated: Agranulocytosis, taste disorder and gynaecomastia were listed as rare side effects. Pancytopenia was added as a very rare side effect and hypomagnesaemia was listed as a side effect of not known frequency. The evidence with regard to hypomagnesaemia in short term use was not deemed sufficient to add an additional safety warning in 4.4. of the SPC for the OTC which are indicated for short-term use only.

	clinical, clinical or pharmacovigilance data				
IG/0079/G	This was an application for a group of variations. 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	24/06/2011	n/a		
IG/0070	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	26/05/2011	n/a	SmPC, Annex II, Labelling and PL	
IG/0043/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.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	02/02/2011	n/a		
IG/0006	A.7 - Administrative change - Deletion of	19/05/2010	n/a		

	manufacturing sites				