Pyramax

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/0036	Update of sections 4.4 and 4.6 of the SmPC with revised recommendations for treatment during pregnancy. The Package Leaflet has been updated accordingly. An updated RMP version 18.2 was agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	05/06/2025		SmPC and PL	SmPC new text The SOH proposes in this application an update of the Product Information and the RMP in the light of recent data provided in the three-yearly update of the Pregnancy Report and two major studies (MiMBa Registry and PYRAPREG trial). The Product Information has been updated to provide the exposure to Pyramax treatment for malaria in pregnant women, to include data on exposure in

[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).

	data				the first trimester of pregnancy, and to amend the wording in section 4.4 and 4.6 of the SmPC for Pyramax tablets accordingly. These results, in absolute and relative terms, do not at this stage indicate any increased risk in adverse pregnancy outcomes or teratogenic effects from the use of Pyramax during pregnancy. However, these data are still limited, particularly concerning exposure to Pyramax during the first trimester of pregnancy. The updates to the SmPC are adequate to mitigate this risk.
IA/0037/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	27/11/2024	n/a		
PSUV/0035	Periodic Safety Update	11/04/2024	n/a		PRAC Recommendation - maintenance
IA/0034/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 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/06/2023	n/a		

	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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
II/0031/G	This was an application for a group of variations. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF B.I.b.2.a - Change in test procedure for AS or	27/10/2022	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0033/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	08/08/2022	n/a		
IB/0030/G	This was an application for a group of variations. 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.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	15/06/2022	n/a		
IB/0029/G	This was an application for a group of variations. B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	15/06/2022		SmPC, Labelling and PL	

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0032/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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	06/06/2022		SmPC	
IB/0027/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.c - Change in the specification parameters	24/05/2022	n/a		

	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 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				
IA/0028/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.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	04/04/2022	n/a		

IB/0026	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/03/2022	n/a		
IAIN/0025/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.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.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)	28/01/2022	n/a		
IB/0024/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	25/01/2022	n/a		

II/0023/G	This was an application for a group of variations. 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	02/12/2021		SmPC and PL	
PSUV/0022	Periodic Safety Update	11/03/2021	n/a		PRAC Recommendation - maintenance
PSUV/0021	Periodic Safety Update	12/03/2020	n/a		PRAC Recommendation - maintenance
PSUV/0020	Periodic Safety Update	14/03/2019	n/a		PRAC Recommendation - maintenance
IB/0019	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	01/05/2018	n/a		
PSUV/0017	Periodic Safety Update	08/03/2018	n/a		PRAC Recommendation - maintenance
PSUV/0016	Periodic Safety Update	14/09/2017	n/a		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0016.
II/0015	Update of sections 4.8 and 5.1 of the SmPC in order to reflect the main efficacy and safety results from the final report from study SP-C-013-11 listed as a category 3 study in the RMP. This is a phase IIIb/IV comparative, randomised, multi-centre, open label, parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of pyronaridine-	13/07/2017		SmPC	In the analysis of the repeat-dose Phase IIIb longitudinal study of 1342 patients treated with Pyramax tablets and granules for oral suspension and examining safety and efficacy of repeat dosing the efficacy findings were similar to those in pivotal trials and were maintained with repeated treatment episodes. In the Phase IIIb longitudinal study Pyramax was

	artesunate, dihydroartemisinin-piperaquine or artemether-lumefantrine or artesunate-amodiaquine over a 2-year period in children and adult patients with acute uncomplicated Plasmodium sp. malaria. In addition, the SOH took the opportunity to make some editorial changes to the product information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				administered to patients experiencing single and repeated episodes of malaria and was shown to be similarly well tolerated on repeat administration as for first administration with repeat administration intervals as short as 28 days. The comparator arms of the study, artemether-lumefantrine or artesunate-amodiaquine, or a second study arm of DHA-piperaquine, also showed similar tolerability between initial and repeat administration. Where transient ALT elevations occurred, the adverse event profile was slightly higher with repeat administration for both adults and children. In Episode 1, the percentage of patients with ALT > 1.5xULN and ≤ 3xULN for the 4 treatment arms was Pyramax 3.9%, artemether-lumefantrine 2.2%, artesunate-amodiaquine 1.2% and DHA-piperaquine 1.6%. In Episode 2+, the percentage of patients with ALT >1.5xULN and ≤ 3xULN for the 4 treatment arms was Pyramax 5.1%, artemether-lumefantrine 2.2%, artesunate-amodiaquine 2.4% and DHA-piperaquine 2.2%. Pyramax compared favourably to the other treatment arms in terms of QTc (Bazett and Fridericia) both on initial or any repeat dose (measured centrally). In Episode 1, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 4.0%, artemether-lumefantrine 10.3%, artesunate-amodiaquine 24.2% and DHA-piperaquine 34.1% and QTc (Fridericia), 0%, 0%, 5% and 7.2% respectively. No Pyramax patients had a QTc >480 msec. In Episode 2+, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 7.2%, artemether-lumefantrine 10%, artesunate-amodiaquine 41.1% and DHA-piperaquine 48.5% and QTc (Fridericia), 1.6%%, 2.9%, 9.55% and 17.6% respectively. No Pyramax patients had a QTc >500 msec.

					Pyramax was administered to patients experiencing single and repeated episodes of malaria and was shown to be similarly well tolerated on repeat administration, as for first administration with repeat administration intervals as short as 28 days. The comparator arms of the study, artemether-lumefantrine or artesunateamodiaquine, or a second study arm of DHA-piperaquine, also showed similar tolerability between initial and repeat administration. Where transient ALT elevations occurred, the adverse event profile was similar with repeat administration for both adults and children based on data associated with the treatment of Episode 1 and any repeat treatment (Episodes 2+) for all treatment arms in terms of liver enzyme classifications for the highest post Day 0 values.
PSUV/0014	Periodic Safety Update	06/04/2017	n/a		PRAC Recommendation - maintenance
PSUV/0013	Periodic Safety Update	02/09/2016	n/a		PRAC Recommendation - maintenance
PSUV/0012	Periodic Safety Update	17/03/2016	n/a		PRAC Recommendation - maintenance
X/0008/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015		SmPC, Labelling and PL	For further information please refer to the published Assessment Report: Pyramax H-W-2319-X-08-AR.
II/0002	Extension of the indication to remove restrictions on repeated courses of treatment in any patient and use only in areas of low transmission with evidence of	19/11/2015		SmPC and PL	For further information please refer to the published Assessment Report: Pyramax H-W-2319-II-02-AR.

	artemisinin resistance. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated in accordance. In addition, the Applicant took the opportunity to implement minor editorial and template-related changes in the annexes. A revised RMP version 12.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUV/0010	Periodic Safety Update	10/09/2015	n/a		PRAC Recommendation - maintenance
IAIN/0011	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	01/07/2015	n/a		
PSUV/0009	Periodic Safety Update	12/03/2015	n/a		PRAC Recommendation - maintenance
PSUV/0007	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IAIN/0006/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.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	24/07/2014		SmPC, Annex II, Labelling and PL	

	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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - 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 PhV system				
II/0003	Update of sections 4.4 and 4.8 of the SmPC in order to reflect the findings of significant rises in transaminases in Caucasian healthy volunteers in follow-up to the assessment of PSUR 2. A further change is made to SmPC section 4.6 following review of the First Annual Report on the Pregnancy Registry. Additional changes are introduced in section 5.2 of the SmPC relating to the long half-life of pyronaridine and the metabolic profiling. Finally, a minor change is made to section 4.2 of the SmPC related to patients with mild or moderate renal impairment. Pyronaridine shows in vitro CYP2D6 inhibitory potential that is confirmed in vivo using metoprolol as CYP2D6 probe. The study shows an increase of	26/06/2014		SmPC	Findings regarding significant transient transaminase rises in Caucasian healthy volunteers treated with Pyramax seem more linked to differences of pharmacokinetics due to non-infected state of healthy volunteers than to the potential difference of metabolic pathways between ethnic origins.

	metoprolol Cmax around 50% but the overall exposure increases to a lesser extent. Caution is therefore advised when co-administering Pyramax with metoprolol given in cardiac failure, notably during the titration phase and a possible dose adjustment may be required. This applies to flecainide and propafenone as well, two antiarrhythmics exclusively metabolised by CYP2D6. As pyronaridine shows in vitro P-gp inhibitory potential, substrates for P-gp such as digoxin and dabigatran may require additional monitoring of blood levels and possible dose adjustment as well. The combination of Pyramax and primaquine has shown neither clinically relevant pharmacokinetic variations nor any impaired tolerance. If needed, the two antimalarial drugs may be co-administered. A pregnancy register to monitor all pregnancies and their outcomes has been set up by the supplier. In the event that a patient is found to be pregnant whilst receiving Pyramax or becomes pregnant within two months of treatment this must be reported to the supplier immediately. Pyronaridine appears to have a large number of potential metabolites, with no clear major metabolic route. Human in vivo metabolite profiling was conducted in blood, urine, and faecal samples from six healthy male volunteers in a microdose radioactivity mass balance study. Pyronaridine (unchanged) and a total of thirteen metabolites were identified in one or more sample matrices. Proposed metabolic pathways include: N-dearylation, oxidation, de-methylation, glucuronidation, cysteine				

	conjugation, acetylation and reduction. C.I.3.z - 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 - Other variation				
PSUV/0001	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IAIN/0005	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	24/04/2014		SmPC	