Pedea

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
IA/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/11/2022		SmPC and PL	To update sections 4.4 and 4.8 of the SmPC and the sections 2 and 4 of the PL to implement the signal recommendation on 'Ibuprofen – Acute generalised exanthematous pustulosis (AGEP)' (EPITT no 19409), adopted at the 5 September 2019 PRAC meeting.

[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

An agency of the European Union

IA/0031	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	30/08/2022	n/a		
II/0030	Please refer to the Recommendations section 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	12/05/2022	n/a		Not applicable
IA/0029/G	This was an application for a group of variations. 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 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	22/04/2021	n/a		
PSUSA/1712/ 202007	Periodic Safety Update EU Single assessment - ibuprofen (indicated in ductus arteriosus)	11/03/2021	n/a		PRAC Recommendation - maintenance
IG/1085/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	16/05/2019	23/04/2020	SmPC, Annex II, Labelling and PL	

	and/or address of a manufacturer/importer responsible for batch release A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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)				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2019	23/04/2020	PL	
IA/0025/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	13/11/2018	n/a		
IA/0024	A.7 - Administrative change - Deletion of manufacturing sites	27/09/2018	n/a		
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2018	23/04/2020	Labelling and PL	
PSUSA/1712/ 201707	Periodic Safety Update EU Single assessment - ibuprofen (indicated in ductus arteriosus)	22/03/2018	22/05/2018		Considering the morbidity and mortality associated with gastric perforation, the suspicion of causality attributed to Pedea by the reporters in 4/5 cases, the existence of a biologically plausible mechanism, and the rarity of the condition amongst all gastrointestinal perforations in the

					neonatal period, the MAH is requested to add the adverse reaction "gastric perforation" in section 4.8 of the SmPC with a frequency "unknown" in order to alert healthcare professionals to the possibility of this specific adverse drug reaction.
IA/0021	A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS	23/11/2017	n/a		
IA/0019/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	11/08/2017	n/a		
IG/0773/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	14/02/2017	05/02/2018	Annex II and PL	
IG/0686	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	12/05/2016	n/a		

	site				
PSUSA/1712/ 201407	Periodic Safety Update EU Single assessment - ibuprofen (indicated in ductus arteriosus)	12/03/2015	n/a		PRAC Recommendation - maintenance
IG/0535	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	06/03/2015	n/a		
II/0014/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy	23/10/2014	n/a		

	of the medicinal product 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 B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
IG/0393	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	20/12/2013	n/a		
IG/0392	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	19/12/2013	10/03/2014	Annex II and PL	
II/0011	Update of section 4.4 of the SmPC, upon request by the CHMP following the assessment of PSUR 7 and PS2 018.1, with wording to emphasise that close attention should be paid to pulmonary pressure if hypoxaemia occurs during or following Pedea	21/03/2013	10/03/2014	SmPC and Annex II	The MAH has submitted a variation to update the SmPC as requested by the CHMP following the assessment of PSUR 7 and PS2 018.1. The MAH has analysed the cumulative cases registered in the global safety database of patients treated with Pedea

	infusion, and update of section 4.8 of the SmPC to reflect that cases of pulmonary hypertension have been reported post-marketing. In addition, the MAH took the opportunity to update annex II in line with the latest QRD template version 8.3. 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				and who experienced pulmonary hypertension (PH) or pulmonary arterial hypertension (PAH). The cumulative review covers the period from 01/01/1990 to 29/03/2012. The degree of prematurity of new-borns and its influence on the risk of PH in neonates were taken into consideration in this cumulative analysis. The review included all patients who experienced a PH event including all those who were enrolled in Pedea clinical studies. Following the assessment of the provided data, the existing warning in section 4.4 of the SmPC regarding pulmonary hypertension has been reinforced to emphasise that if hypoxemia occurs during or following Pedea infusion, close attention should be paid to pulmonary pressure. Further, the current text in section 4.8 has been updated to mention that post-marketing cases of pulmonary hypertension have also been reported which were possibly related to Pedea administration. No changes to the Package Leaflet are considered necessary as these issues are already sufficiently covered. Finally, the MAH has updated annex II in line with the latest QRD template version 8.3, which is acceptable. The variation does not have any impact on the benefit/risk balance for Pedea, which remains positive for the approved indications.
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2012	10/03/2014	PL	
IA/0009	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	19/04/2012	n/a		

N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/02/2012	10/03/2014	PL	
II/0007	Changes to the specifications of the active substance and as a consequence, change to the specifications of the finished product Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	24/09/2009	09/10/2009		
R/0006	Renewal of the marketing authorisation.	29/05/2009	24/07/2009	SmPC, Labelling and PL	Based on the CHMP review of the available information and on the basis of the re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Pedea continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. PSURs will now be submitted every 3 years.
IA/0005	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	19/09/2007	n/a	SmPC, Annex II, Labelling and PL	
II/0004	Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	24/11/2006	SmPC and PL	Further to the CHMP request following the 3rd PSUR assessment, the MAH updated Section 4.8 to include acute renal failure. The PL was updated accordingly.

II/0002	Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	29/03/2006	SmPC and PL	Following the assessment of the 1st PSUR by the CHMP, the MAH updated sections 4.4 and 4.5 of the SPC to include information on the potential interaction with aminoglycosides. As ibuprofen may decrease the clearance of aminoglycosides, their co-administration may increase the risk of nephrotoxicity and ototoxicity and strict surveillance of their serum levels is recommended during co-administration with ibuprofen. The corresponding section 2 of the Package Leaflet has been updated accordingly.
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	03/03/2006	n/a		
II/0001	Update of or change(s) to the pharmaceutical documentation	27/07/2005	26/08/2005	SmPC and PL	