Orphacol

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
IAIN/0052/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/importer	15/05/2023		SmPC, Annex II, Labelling and PL	

[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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	responsible for batch release				
PSUSA/10208 /202209	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0051/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	05/04/2023	n/a		
S/0048	9th annual re-assessment.	23/02/2023	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that the marketing authorisation under exceptional circumstances of Orphacol should be maintained.
IAIN/0050/G	This was an application for a group of variations. 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 A.1 - Administrative change - Change in the name and/or address of the MAH	13/01/2023		SmPC, Annex II, Labelling and PL	

IB/0047	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/08/2022	n/a		
IA/0046	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	05/07/2022	n/a		
II/0045	Update of section 4.5 of the SmPC in order to update the existing information regarding concomitant use of cholic acid (the active substance of Orphacol) and ursodeoxycholic acid based on scientific literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/05/2022		SmPC and PL	Ursodeoxycholic acid competitively inhibits absorption of other bile acids, including cholic acid, and replaces them in the enterohepatic pool, reducing the effectiveness of negative feedback inhibition on bile acid synthesis provided by oral cholic acid. For patients who are prescribed a combination of ursodeoxycholic acid and cholic acid in single doses, the administration of both medicinal products should be separated: one product should be given in the morning and the other product should be given in the evening, regardless of which medicinal product is given first. For those patients, who are prescribed a combination of ursodeoxycholic acid and cholic acid, in divided doses of cholic acid and/or ursodeoxycholic acid over the day, the administration of these medicinal products should be separated by several hours. For more information, please refer to the Summary of Product Characteristics.
II/0044	Update of sections 4.3 and 4.5 of the SmPC in order to extend the currently existing contra-indication with phenobarbital to include primidone based on scientific literature. The Package Leaflet is updated	19/05/2022		SmPC, Labelling and PL	Phenobarbital and primidone, which is partially metabolized into phenobarbital, antagonise the effect of cholic acid. Use of phenobarbital or primidone in patients with 3β-Hydroxy-Δ5-C27-steroid oxidoreductase deficiency or

	accordingly. In addition, MAH took the opportunity to submit a combined SmPC for both dosages, 50 mg and 250 mg and to introduce editorial changes and update the contact details of the local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Δ4-3-Oxosteroid-5β-reductase deficiency treated with cholic acid is contraindicated. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10208 /202109	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	07/04/2022	n/a		PRAC Recommendation - maintenance
S/0042	8th annual re-assessment	24/03/2022	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation under exceptional circumstances of Orphacol should be maintained.
II/0040	Submission of an updated RMP version 4.0 to bring it in line with the new RMP template. At the same time, the wording of the additional risk minimisation measures has been updated and the already approved protocol for the ongoing patient surveillance database study has been included in the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	10/06/2021	n/a		

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IB/0041/G	This was an application for a group of variations. 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 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 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.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 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	27/05/2021	n/a		
PSUSA/10208	Periodic Safety Update EU Single assessment - cholic	09/04/2021	n/a		PRAC Recommendation - maintenance

/202009	acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)				
S/0038	7th annual re-assessment	25/02/2021	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation under exceptional circumstances of Orphacol should be maintained.
IA/0037	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)	08/09/2020	n/a		
S/0033	6th annual re-assessment.	28/05/2020	27/07/2020	SmPC and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Orphacol should be maintained under exceptional circumstances. Cases of liver disorder including cases with fatal outcome on different uses of cholic acid were reported. Although conclusive causality cannot be established for the retrieved hepatotoxicity cases due to the patients pre-existing liver impairment and overall medical history, the role of Cholic acid in liver function deterioration could not be excluded in any of these cases. Considering the safety information for the approved use is rather limited a strengthened warning was included in the product information that treatment with cholic acid in patients with pre-existing hepatic impairment should be

					given under close monitoring and, for all patients, should be stopped if abnormal hepatocellular function does not improve within 3 months of the initiation of treatment. The update of the product information affects sections 4.4 and 4.2 (for a cross reference to 4.4) of the SmPC. The package leaflet was updated accordingly.
IB/0036	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	28/05/2020	n/a		
PSUSA/10208 /201909	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0035	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	13/03/2020	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/01/2020	27/07/2020	PL	
IG/1165	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)	10/11/2019	n/a		
IG/1136/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name	22/08/2019	27/07/2020	Annex II and PL	

	and/or address of a manufacturer/importer 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/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/07/2019	27/07/2020	PL	
PSUSA/10208 /201809	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	11/07/2019	n/a		PRAC Recommendation - maintenance
S/0026	5th annual re-assessment.	26/04/2019	04/07/2019	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that the marketing authorisation under exceptional circumstances of Orphacol should be maintained.
II/0025	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	29/05/2019	n/a		

	Introduction of a manufacturer of the AS supported by an ASMF				
R/0028	Renewal of the marketing authorisation.	28/03/2019	24/04/2019		
PSUSA/10208 /201709	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	12/04/2018	n/a		PRAC Recommendation - maintenance
S/0022	Annual re-assessment.	22/02/2018	n/a		
IB/0023/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.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 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 B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.I.d.1.a.4 - Stability of AS - Change in the re-test	02/02/2018	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IA/0021	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	04/08/2017	08/05/2018	SmPC	
IB/0020/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 C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/05/2017	08/05/2018	SmPC, Annex II, Labelling and PL	
PSUSA/10208 /201609	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	06/04/2017	n/a		PRAC Recommendation - maintenance
IB/0019	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	31/01/2017	n/a		
S/0016	Annual re-assessment.	26/01/2017	n/a		

PSUSA/10208 /201603	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	29/09/2016	n/a		PRAC Recommendation - maintenance
PSUSA/10208 /201509	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	14/04/2016	n/a		PRAC Recommendation - maintenance
S/0012	2nd annual re-assessment	28/01/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Orphacol should be maintained.
IB/0013/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/11/2015	n/a		
PSUSA/10208 /201503	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	08/10/2015	n/a		PRAC Recommendation - maintenance
PSUSA/10208 /201409	Periodic Safety Update EU Single assessment - cholic acid (oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication)	10/04/2015	n/a		PRAC Recommendation - maintenance

S/0008	1st Annual Re-assessment	22/01/2015	19/03/2015	SmPC	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH concluded that the benefit/risk profile of the medicinal product continued to be positive. As the specialisation experienced "hepatologist" does not exist in all member states experienced "gastroenterologist" was added in 4.2 to the specialists initiating and monitoring the treatment. Editorial changes were made to 4.6 of the SmPC.
IB/0007	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/12/2014	n/a		
IB/0009/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	04/11/2014	n/a		
PSUV/0004	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IA/0006/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	03/10/2014	n/a		

	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 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				
IAIN/0005	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	23/07/2014	n/a		
IA/0003/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	28/02/2014	n/a		

	manufacturer				
IB/0001/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/importer responsible for batch release 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.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	11/11/2013	16/12/2014	SmPC, Annex II, Labelling and PL	
IAIN/0002	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	24/10/2013	n/a		