Lupkynis

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
PSUSA/11020 /202401	Periodic Safety Update EU Single assessment - voclosporin	19/09/2024	18/11/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/11020/202401.
IA/0016/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	22/08/2024	n/a		

[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

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0013	Update of sections 4.6 and 5.2 of the SmPC in order to update breast-feeding information based on final results from study AUR-VCS-2021-04. This study is a single-center, open-label, Phase 1, lactation study to investigate the amount of voclosporin excreted in breast milk following a single oral dose of 23.7 mg voclosporin in healthy, lactating, female volunteers. The Package Leaflet is updated accordingly. The updated RMP version 5.0 is agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/06/2024	18/11/2024	SmPC and PL	SmPC Section 4.6 is updated to indicate that in a study in 12 lactating subjects, the highest estimated voclosporin dose ingested by a fully breastfed infant was 1.4% of maternal weight-adjusted dose (see section 5.2). The effect of voclosporin on newborns/infants is unknown. SmPC Section 5.2 is updated to indicate that following a single 23.7 mg dose of voclosporin in lactating volunteers (see section 4.6), an average of 0.00472 mg voclosporin was excreted in breast milk in 48h, with 80% being excreted within 12h. Data showed that the voclosporin milk to maternal blood exposure ratio was in the range of 0.42 to 0.95. For a breastmilk intake of 200 mL/kg/day, the highest relative infant dose was 1.4% of maternal weight-adjusted dose. For more information, please refer to the Summary of Product Characteristics.
IB/0015/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	27/05/2024	n/a		
PSUSA/11020 /202307	Periodic Safety Update EU Single assessment - voclosporin	08/02/2024	n/a		PRAC Recommendation - maintenance
II/0010	Submission of the final study report from AUR-VCS-	14/12/2023	n/a		The AURORA 2 biopsy substudy was designed to assess

	2016-02 (AURORA 2) Kidney Biopsy Substudy, listed as a category 3 study in the RMP. The AURORA 2 extension trial included an optional biopsy substudy which was designed to assess renal histology from tissue samples taken prior to and after approximately 18 months of randomized treatment with voclosporin or placebo. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				renal histology. It provides data on the long-term safety of voclosporin given the concern on CNI-induced nephrotoxicity. Although some concerns are raised because of the observed increase in chronicity index observed in the voclosporin group, it is acknowledged that the study is small and that the distinction between LN-induced fibrosis and sclerosis and CNI-induced nephrotoxicity is very difficult. No firm conclusions can be made on an association between voclosporin and CNI-induced nephrotoxicity, although it is reasonable to assume that voclosporin does not differ from other CNIs when it comes to the risk for chronic nephrotoxicity. Further data are expected from an observational PASS to further characterise and quantify long-term safety profile of Lupkynis, focusing on the risks of malignancy, neurotoxicity and nephrotoxicity.
IA/0012	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	06/12/2023	n/a		
PSUSA/11020 /202301	Periodic Safety Update EU Single assessment - voclosporin	31/08/2023	n/a		PRAC Recommendation - maintenance
II/0005	Update of sections 4.5 and 5.2 of the SmPC in order to update pharmacokinetic and safety information based on final results from study AUR-VCS-2021-02, safety data from Phase 2 and 3 studies submitted as part of the initial marketing authorisation application and post-marketing data. AUR-VCS-2021-02 is a single-center, open-label, Phase 1 study to investigate the effect of voclosporin on the pharmacokinetics of simvastatin and simvastatin acid	20/07/2023	16/02/2024	SmPC	Voclosporin is an inhibitor of OATP1B1 and OATP1B3 transporters. In the study AUR-VCS-2021-02 / Statin-DDI, the concomitant administration of a single 40 mg dose of simvastatin with 23.7 mg BID voclosporin increased Cmax and AUC of the active metabolite simvastatin acid (a sensitive OATP1B1/OATP1B3 substrate) by 3.1-fold and 1.8-fold, respectively. In the same study, exposure of the parent drug simvastatin (which is also a BCRP substrate) was unaffected in terms of AUC while its Cmax increased by

	in healthy male and female subjects aged 18 to 55 years. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				1.6-fold, which could potentially be attributed to an interaction between intestinal BCRP and voclosporin. It is recommended in the SmPC of Lupkynis to monitor for adverse events such as myopathy and rhabdomyolysis when OATP1B1/OATP1B3 substrates (e.g., simvastatin, atorvastatin, pravastatin, rosuvastatin) are used concomitantly with voclosporin. Voclosporin inhibits breast cancer resistance protein (BCRP) in vitro. A clinically relevant inhibition of intestinal BCRP cannot be excluded and voclosporin may increase the concentration of these substrates in vivo. It is recommended in the SmPC of Lupkynis to monitor use of BCRP substrates where small concentration changes may lead to serious toxicity (e.g., rosuvastatin) when used concomitantly with voclosporin. For more information, please refer to the Summary of Product Characteristics.
IB/0006	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/05/2023	n/a		
IB/0007/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.d.1.a.4 - Stability of AS - Change in the re-test	03/05/2023	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF				
IB/0004	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	02/02/2023	16/02/2024	SmPC, Labelling and PL	Product information updated to add a new pack-size of 576 capsules in carton for Lupkynis 7.9 mg soft capsules (EU/1/22/1678/002).
IB/0002	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	10/01/2023	n/a		
IB/0003	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/01/2023	n/a		
IA/0001	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	11/11/2022	n/a		