GIVLAARI

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/10839 /202211	Periodic Safety Update EU Single assessment - givosiran	08/06/2023	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. Update of section 5.3 of the SmPC based on final	08/06/2023		SmPC 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).

	results from study AS1-GLP18-007 listed as a category 3 study in the RMP; This is a 104-week Subcutaneous Injection Carcinogenicity Study in Sprague Dawley Rats. Update of section 5.3 of the SmPC based on final results from study AS1-GLP18-004; This is a 26-week Subcutaneous Injection Carcinogenicity Study in TgRasH2 Mice. The RMP version 2.6 has also been submitted. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0015	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)	12/04/2023	n/a		
PSUSA/10839 /202205	Periodic Safety Update EU Single assessment - givosiran	01/12/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10839 /202111	Periodic Safety Update EU Single assessment - givosiran	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0006	Update of SmPC section 4.8 to add 'blood	05/05/2022	24/04/2023	SmPC and PL	Blood homocysteine levels may be increased in patients

	homocysteine increase' as a new ADR with the frequency 'common' and SmPC section 4.4 to add a related warning. The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives for Malta and Cyprus in the Package Leaflet. An updated RMP version 1.4 was agreed during the procedure: consequences of blood homocysteine increase is being added as a new important potential risk, the clinical and post-marketing exposure is being updated and the due dates for ALN-AS1-002 and ALN-AS1-003 final study reports are being revised. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with acute hepatic porphyria (AHP), vitamin deficiencies, or chronic kidney disease. During treatment with givosiran, increases in blood homocysteine levels have been observed compared to levels before treatment. The clinical relevance of the elevations in blood homocysteine during treatment with givosiran is unknown. However, homocysteine elevations have been previously associated with an increased risk of thromboembolic events. Measurement of blood homocysteine levels prior to initiating treatment and monitoring for changes during treatment with givosiran is recommended. In patients with elevated homocysteine levels homocysteine-lowering therapy can be considered. For more information, please refer to the Summary of Product Characteristics.
IB/0009/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 A.7 - Administrative change - Deletion of manufacturing sites	08/02/2022	n/a		
PSUSA/10839 /202105	Periodic Safety Update EU Single assessment - givosiran	02/12/2021	n/a		PRAC Recommendation - maintenance

IAIN/0008/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.f.1.e - Stability of FP - Change to an approved stability protocol	22/11/2021	n/a		
PSUSA/10839 /202011	Periodic Safety Update EU Single assessment - givosiran	24/06/2021	18/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10839/202011.
II/0004/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	09/04/2021	18/08/2021	SmPC and PL	The SmPC section 6.5 has been updated accordingly as follows: Glass vial with a fluoropolymer-coated rubber stopper and a flip-off aluminium seal. Each vial contains 1 mL solution for injection.
PSUSA/10839 /202005	Periodic Safety Update EU Single assessment - givosiran	14/01/2021	n/a		PRAC Recommendation - maintenance

IAIN/0003/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 A.6 - Administrative change - Change in ATC Code/ATC Vet Code	26/11/2020	18/08/2021	SmPC, Annex II, Labelling and PL	
IB/0001/G	This was an application for a group of variations. 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 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	06/07/2020	n/a		