Spherox

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/0031/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.a - Administrative change - Change in the name	16/02/2023		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).

	and/or address of a manufacturer/importer responsible for batch release 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.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.1 - Administrative change - Change in the name and/or address of the MAH				
PSUSA/10630 /202207	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	09/02/2023	n/a		PRAC Recommendation - maintenance
T/0030	Transfer of Marketing Authorisation	05/12/2022	10/01/2023	SmPC, Labelling and PL	
IB/0028	B.II.b.z - Change in manufacture of the Finished Product - Other variation	02/09/2022	n/a		
IB/0027	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	08/08/2022	n/a		

R/0024	Renewal of the marketing authorisation.	24/02/2022	29/04/2022	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Spherox in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0026	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	07/03/2022	n/a		
PSUSA/10630 /202107	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	10/02/2022	n/a		PRAC Recommendation - maintenance
II/0020	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/05/2021	28/06/2021	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0020'
IB/0023	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	21/05/2021	n/a		
II/0022	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	28/06/2021	SmPC and Annex II	
II/0021/G	This was an application for a group of variations.	22/04/2021	28/06/2021	Annex II and	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product			PL	
PSUSA/10630 /202007	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	11/02/2021	n/a		PRAC Recommendation - maintenance
PSUSA/10630	Periodic Safety Update EU Single assessment -	17/09/2020	20/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/202001	spheroids of human autologous matrix-associated chondrocytes				the variation to terms of the Marketing Authorisation(s)' for PSUSA/10630/202001.
IB/0018/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.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)	01/10/2020	n/a		
II/0016	The RMP has been updated in accordance with GVP Module V Rev. 2 template. The educational materials described in Annex II have been updated with editorial changes accordingly. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/05/2020	09/10/2020	Annex II	The RMP has been updated in accordance with GVP Module V Rev. 2 template. No new safety concerns have been documented and therefore no new risk minimisation measures are required. The educational materials described in Annex II have been updated with editorial changes: only information on the key elements of the training material for surgeons/ other HCPs and the prescriber checklist is provided, not the entire document of the training material.
II/0015	Update of section 4.8 and 5.1 of the SmPC and relevant sections of the PL following the 48-month follow up data for trial cod 16 HS 13, a study assessing the long-term efficacy and safety of Spherox. C.I.4 - Change(s) in the SPC, Labelling or PL due to	28/05/2020	09/10/2020	SmPC and PL	MAH submitted the 48-month follow-up data for study cod 16 HS 13. The ongoing Study cod 16 HS 13 is a prospective, randomised, open-label (central reading by blinded radiologist) active-controlled, multicentre trial to compare the efficacy and safety of treatment with ACT3D-CS to microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm2. Patients will

	new quality, preclinical, clinical or pharmacovigilance data				be followed for 60 months. Overall, the Phase 3 trial with microfracture (MF) as comparator continued to indicate consistent outcomes for Spherox compared to MF. Updated safety results for study 16 HS 13 (48 month follow-up) were also provided. The overall safety profile for Spherox remains unchanged. The PI was updated to reflect bone marrow oedema as common adverse reaction and to reflect the study results.
PSUSA/10630 /201907	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	16/01/2020	n/a		PRAC Recommendation - maintenance
IB/0014	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	14/01/2020	n/a		
IB/0012	B.II.e.z - Change in container closure system of the Finished Product - Other variation	08/01/2020	n/a		
IA/0013	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	12/12/2019	n/a		
IA/0010	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	17/10/2019	n/a		

II/0008	The MAH has submitted a prospective process validation study using batches manufactured with a well-controlled process and to collect quality data from a sufficient number of batches to demonstrate consistency, quality and genetic stability of the cells in the finished product which was a condition to the Marketing Authorisation. Annex II of the Marketing Authorisation is updated to remove the corresponding obligation. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	19/09/2019	09/10/2020	Annex II	
II/0005/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC to reflect the study results of the 36-month follow up data for trial cod 16 HS 13 and the final study report with 60-month follow-up data for trial cod 16 HS 14. Study cod 16 HS 13, is a Prospective, randomised, open label, multicentre Phase-III clinical trial to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product co.don chondrosphere (ACT3D-CS) with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm2.	19/09/2019	09/10/2020	SmPC and PL	Results from both studies confirmed that outcomes were consistent with previous submitted data These results were reflected in section 5.1. In study cod 16 HS 14, the primary efficacy variable, change of overall KOOS from baseline at 60 months, was on average (SD) 19.9±18.0, very similar to the 48-month data (mean: 20.1 ±17.3), showing a clinically relevant and sustained improvement in KOOS. In line with previous reports, no relevant differences between the low, medium, and high dose were noted. KOOS subscores were also consistent with previous data. MOCART scores at 60 months were also consistent with previous data i.e. maintained improvement with no evidence of a dose response. The overall MOCART score at 60 months for

	Study cod 16 HS 14, is a Prospective, randomised, open label, multicentre Phase-II clinical trial to investigate the efficacy and safety of the treatment of large defects (4-10 cm2) with three different doses of the autologous chondrocyte transplantation product co.don chondrosphere (ACT3D-CS) in subjects with cartilage defects of the knee. 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				all doses combined was 75.1±14.5, similar to previous data. In study cod 16 HS 13 results for overall KOOS and change of overall KOOS from baseline at 36 months were presented. For the patients treated with ACT3D-CS the mean overall KOOS score was 83.2 ± 14.9 as compared with 76.3 ± 17.1 for MF. The mean change from baseline was +26.6 ± 16.2 for patients in the ACT3D-CS group and 24.5 ± 16.7 for those in the MF group. Overall, this is in line with the previous data. KOOS subscores also showed a pattern that was consistent with previous data. The MOCART score at 36 months was respectively 75.0 ± 13.4 and 78.3 ± 12.6 for the ACT3D-CS and microfracture groups showing consistency over time. No new safety concerns were identified in the data presented for both studies. Section 4.8 of the SmPC and relevant section of the PL was updated to differentiate any surgery-related event terms and depicting them separately.
PSUSA/10630 /201901	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	11/07/2019	n/a		PRAC Recommendation - maintenance
IA/0006/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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	27/03/2019	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10630 /201807	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	17/01/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10630 /201801	Periodic Safety Update EU Single assessment - spheroids of human autologous matrix-associated chondrocytes	12/07/2018	n/a		PRAC Recommendation - maintenance
II/0002/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	28/06/2018	11/04/2019	SmPC and PL	
II/0001	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/04/2018	11/04/2019	Annex II	