Zejula

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
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/01/2024		PL	
II/0044	Submission of an updated modelling report with the results from the population pharmacokinetic and exposure-response modelling exercises as requested	14/12/2023	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

	as part of variation II/0019 (REC 007). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0049/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	24/11/2023		SmPC, Labelling and PL	
IA/0048	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)	09/11/2023	n/a		
IB/0047	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)	06/11/2023		SmPC	
PSUSA/10655 /202303	Periodic Safety Update EU Single assessment - niraparib	26/10/2023	n/a		PRAC Recommendation - maintenance
IA/0045/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	31/07/2023	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IAIN/0041/G	This was an application for a group of variations. B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	07/07/2023	n/a		
IB/0043	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	26/06/2023	n/a		
IAIN/0042	B.II.b.1.a - Replacement or addition of a	19/06/2023	n/a		

	manufacturing site for the FP - Secondary packaging site				
II/0037	Update of sections 4.2 and 5.2 of the SmPC in order to update recommendations regarding food intake and information on absorption based on results from food effect study 3000-01-004 Stage 3. The package leaflet has been updated accordingly. Furthermore, minor corrections have been made to the product information to reflect that film-coated tablets are provided in blisters. Annex A has been revised accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2023	31/05/2023	SmPC and PL	Following a high-fat meal in patients with solid tumours, the Cmax and AUCinf of niraparib tablets increased by 11% and 28%, respectively, as compared with fasting conditions. It is advised to take Zejula tablets without food (at least 1 hour before or 2 hours after a meal) or with a light meal. For more information, please refer to the Summary of Product Characteristics.
IB/0039	C.z - Safety, Efficacy, Pharmacovigilance changes - Other variation	13/04/2023	n/a		
IA/0038	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)	14/02/2023	n/a		
II/0033	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning and add MDS/AML to the list of adverse drug reactions (ADRs) with frequency common, and update of section 5.1 based on final results from NOVA study (213356); this is a Phase 3 Randomized double-blind trial of	15/12/2022	31/05/2023	SmPC and PL	In Study NOVA, secondary efficacy endpoints included chemotherapy free interval (CFI), time to first subsequent therapy (TFST), PFS after the first subsequent therapy (PFS2), and OS. At the final analysis, the median PFS2 in the gBRCAmut cohort was 29.9 months for patients treated with niraparib

	maintenance with niraparib versus placebo in patients with platinum sensitive relapsed ovarian cancer. In addition, the MAH took this opportunity to update sections 4.4 and 4.6 to update information on contraception based on EMA and CTFG recommendations and to make minor editorial changes in the SmPC. The Package Leaflet is updated accordingly. The RMP version 6.0 is approved. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				compared to 22.7 months for patients on placebo (HR = 0.70; 95% CI: 0.50, 0.97). The median PFS2 in the non-gBRCAmut cohort was 19.5 months for patients treated with niraparib compared to 16.1 months for patients on placebo (HR = 0.80; 95% CI: 0.63, 1.02). At the final analysis of overall survival, the median OS in the gBRCAmut cohort (n = 203) was 40.9 months for patients treated with niraparib compared with 38.1 months for patients on placebo (HR = 0.85; 95% CI: 0.61, 1.20). The cohort maturity for the gBRCAmut cohort was 76%. The median OS in the non-gBRCAmut cohort (n = 350) was 31.0 months for patients treated with niraparib compared with 34.8 months for patients on placebo (HR = 1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-gBRCAmut cohort was 79%. Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and post-marketing. In the NOVA trial, the incidence of MDS/AML was higher in the gBRCAmut cohort (7.4%) than in the non-gBRCAmut cohort (1.7%). For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed Zejula treatment should be discontinued and the patient treated appropriately. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10655 /202203	Periodic Safety Update EU Single assessment - niraparib	27/10/2022	n/a		PRAC Recommendation - maintenance

R/0034	Renewal of the marketing authorisation.	19/05/2022	18/07/2022	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 Zejula in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0036/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 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	22/06/2022	31/05/2023	Annex II and PL	
X/0029	Annex I_2.(d) Change or addition of a new pharmaceutical form	24/03/2022	30/05/2022	SmPC, Annex II, Labelling and PL	
II/0032/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/10/2021	n/a		

PSUSA/10655 /202103	Periodic Safety Update EU Single assessment - niraparib	28/10/2021	n/a		PRAC Recommendation - maintenance
IA/0031	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	09/08/2021	30/05/2022	SmPC and PL	
PSUSA/10655 /202009	Periodic Safety Update EU Single assessment - niraparib	20/05/2021	16/07/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10655/202009.
II/0024	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include information and dosing recommendation for patients with moderate hepatic impairment and a warning on the risk of increased exposure of niraparib in patients with severe hepatic impairment based on final results from hepatic study 3000-01-003 (HEPATIC). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes in SmPC section 4.4. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	01/06/2021	SmPC and PL	No dose adjustment is needed in patients with mild hepatic impairment (either aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin (TB) ≤ ULN or any AST and TB > 1.0 x – 1,5 x ULN). For patients with moderate hepatic impairment (any AST and TB > 1.5 x - 3 x ULN) the recommended starting dose of Zejula is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB > 3 x ULN). Patients with severe hepatic impairment could have increased exposure of niraparib based on data from patients with moderate hepatic impairment and should be carefully monitored.
IB/0028/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	20/04/2021	n/a		

	manufacturer of a novel excipient B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				

IAIN/0027/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 A.7 - Administrative change - Deletion of manufacturing sites 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	05/03/2021	01/06/2021	Annex II and PL	
IA/0026	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	11/12/2020	n/a		
PSUSA/10655 /202003	Periodic Safety Update EU Single assessment - niraparib	29/10/2020	n/a		PRAC Recommendation - maintenance
II/0019	Extension of indication to include the use of Zejula as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The MAH is also taking the opportunity to make minor corrections throughout the PI. The	17/09/2020	27/10/2020	SmPC and PL	Please refer to Scientific Discussion 'Zejula-H-C-004249-II-19'

	Package Leaflet is updated in accordance. Version 5.0 of the RMP to add the new indication, bring it in line with the RMP template Rev. 2.0.1 and update due dates for category 3 studies has been accepted. Annex II is updated with a new post-authorisation efficacy study (PAES). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0020	Update of section 4.8 of the SmPC in order to add hypersensitivity, confusional state, and pneumonitis to the list of adverse drug reactions (ADRs) with the frequency "common", "uncommon" and "uncommon" respectively based on safety evaluations; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2020	27/10/2020	SmPC and PL	
II/0021	Update of section 4.5 of the SmPC in order to add pharmacokinetic interaction information based non-clinical drug-drug interaction (DDI) studies. In addition, the MAH took the opportunity to update section 5.3 of the SmPC in line with the SmPC guideline. The requested variation proposed amendments to the Summary of Product Characteristics.	25/06/2020	27/10/2020	SmPC	Information on multidrug resistance-associated protein 2 (MRP2) has been included in the SmPC based on in vitro results. Niraparib and the major primary metabolite M1 are not substrate of MRP2. Niraparib is not an inhibitor of MRP2. Also, M1 does not appear to be an inhibitor of MRP2. Furthermore, the SmPC is updated to reflect the results from an UGT inhibition study in which niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1, UGT1A4, UGT1A9, and UGT2B7) up to 200 □M in vitro.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10655 /201909	Periodic Safety Update EU Single assessment - niraparib	30/04/2020	25/06/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10655/201909.
IAIN/0022/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 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	30/04/2020	27/10/2020	Annex II and PL	
T/0016	Transfer of Marketing Authorisation	19/12/2019	31/01/2020	SmPC, Labelling and PL	
IB/0018	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	30/01/2020	n/a		
IB/0015/G	This was an application for a group of variations.	08/11/2019	n/a		

	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.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.e.1.z - Change in immediate packaging of the finished product - Other variation				
PSUSA/10655 /201903	Periodic Safety Update EU Single assessment - niraparib	03/10/2019	n/a		PRAC Recommendation - maintenance
IB/0014	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)	24/09/2019	31/01/2020	SmPC	
PSUSA/10655 /201809	Periodic Safety Update EU Single assessment - niraparib	26/04/2019	20/06/2019	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10655/201809.
IA/0012/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.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	23/05/2019	n/a		

	New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer 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.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.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/02/2019	n/a		
IAIN/0009/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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	20/12/2018	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
T/0007	Transfer of Marketing Authorisation	12/11/2018	17/12/2018	SmPC, Labelling and PL	
IA/0008/G	This was an application for a group of variations. 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) B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	05/12/2018	n/a		
PSUSA/10655 /201803	Periodic Safety Update EU Single assessment - niraparib	04/10/2018	n/a		PRAC Recommendation - maintenance
IB/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2018	n/a		

IB/0003/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	06/07/2018	n/a		

	material/intermediate/reagent - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition				
IA/0002/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	19/02/2018	n/a		
IB/0001/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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	19/12/2017	17/12/2018	SmPC, Labelling and PL	