Yondelis

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
II/0063	Update of section 4.8 of the SmPC in order to revise the frequency of ADRs based on a pooled safety analysis. the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2 Rev. 1	22/07/2021		SmPC and PL	SmPC new text: The frequency of the ADRs insomnia and arthralgia were changed from very common to common. In addition some small figure changes were made to the summary of safety profile in section 4.8. For more information please refer to the Summary of

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Product Characteristics.
PSUSA/3001/ 202009	Periodic Safety Update EU Single assessment - trabectedin	09/04/2021	n/a		PRAC Recommendation - maintenance
II/0061	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	11/02/2021	n/a		
A20/0060	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 21 February 2020 the opinion of the European Medicines Agency further to review of study 3306 and its impact on the benefit-risk balance of the ovarian cancer indication. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Yondelis and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.	23/07/2020	24/09/2020	SmPC	Please refer to the assessment report: Yondelis EMEA/H/A-20/1493/C/0773/0060
PSUSA/3001/ 201909	Periodic Safety Update EU Single assessment - trabectedin	17/04/2020	n/a		PRAC Recommendation - maintenance

II/0058	Update of section 4.4 of the SmPC in order to add a warning based on results from study Cardiac Safety Report [Protocols ET743-SAR-3007, ET743-OVA-301, ET743-OVC-3006; Phase 3. JNJ-17027907; R270741 (trabectedin)] following the PSUSA procedure EMEA/H/C/PSUSA/00003001/201809; the Package Leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	12/12/2019	24/09/2020	SmPC and PL	Patients should be monitored for cardiac-related adverse events or myocardial dysfunction. A thorough cardiac assessment including determination of left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition scan (MUGA) should be conducted before initiation of trabectedin and at 2 to 3-month intervals thereafter until trabectedin is discontinued. Patients with LVEF less than the lower limit of normal (LVEF < LLN), prior cumulative anthracycline dose of >300mg/m2, aged >65 years, or a history of cardiovascular disease (especially in those with cardiac medication) may be at increased risk of cardiac dysfunction at treatment with trabectedin as monotherapy or in combination with doxorubicin. For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥15% or <LLN with an absolute decrease of ≥5%), trabectedin should be discontinued.”
PSUSA/3001/ 201809	Periodic Safety Update EU Single assessment - trabectedin	11/04/2019	n/a		PRAC Recommendation - maintenance
IB/0056/G	This was an application for a group of variations. 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) B.I.b.1.d - Change in the specification parameters	15/08/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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) 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) B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
PSUSA/3001/201709	Periodic Safety Update EU Single assessment - trabectedin	26/04/2018	25/06/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3001/201709.
IB/0055	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	25/05/2018	03/05/2019	SmPC and PL	

II/0051	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	19/10/2017	SmPC	Update of section 4.2, 4.4 and 5.2 of the SmPC to include updated information on use of trabectedin in patients with hepatic impairment following completion of study ET743-OVC-1004 "An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction". The systemic exposure to trabectedin is on average approximately doubled in patients with hepatic impairment. Liver function tests should be monitored during treatment with Yondelis as dose adjustments may be indicated.
PSUSA/3001/ 201609	Periodic Safety Update EU Single assessment - trabectedin	21/04/2017	19/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3001/201609.
IB/0052	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/06/2017	n/a		
II/0049/G	This was an application for a group of variations. C.I.4 - Update of section 5.2 of the SmPC in order to introduce pharmacokinetic data as a result of completion of study Study 10045020 - A phase I pharmacokinetic study to assess the tolerability of trabectedin administered as a continuous intravenous infusion over 24 hours every 21 days in Japanese patients with soft tissue sarcoma. The Package leaflet has been updated accordingly. C.I.4 - Update of section 5.1 of the SmPC in order to introduce pharmacodynamic data as a result of	07/07/2016	19/06/2017	SmPC, Labelling and PL	Submission of clinical study report 10045020 phase 1 pharmacokinetics study of trabectedin given as a 24-h continuous infusion in Japanese patients with advanced soft-tissue sarcoma and submission of study report 10045030 open-label, multicenter phase II Study of trabectedin in Japanese Patients with Translocation-related Sarcomas after standard chemotherapy in comparison with best supportive care (BSC). Section 5.1 "Pharmacodynamic properties" (in subsection "Clinical efficacy") and section 5.2 "Pharmacokinetic properties" (in subsection "Special populations") of the SmPC has been updated with the aim to include the results of these studies. The Package Leaflet has been updated accordingly.

	completion of study Study 10045030 - A phase II Study of trabectedin in Japanese Patients with Translocation-related Sarcomas. In addition, the marketing authorisation holder took the opportunity to introduce changes in Annex IIIA and IIIB including the safety feature. 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				
II/0048	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	19/06/2017	SmPC, Labelling and PL	
PSUSA/3001/201509	Periodic Safety Update EU Single assessment - trabectedin	28/04/2016	29/06/2016		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3001/201509.
II/0045	As requested following the assessment of the PSUR, update of sections 4.6 and 5.3 of the SmPC regarding pregnancy information following final non-clinical study report PBC040-101. The PL is updated accordingly. In addition, the MAH took the opportunity to revise the PI in compliance with the last QRD template version 9.1 and combined the 2 SmPCs as recommended.	17/12/2015	29/06/2016	SmPC, Annex II and PL	Following the assessment of non-clinical study PBC040-101, sections 4.6 the SmPC was updated to mention that trabectedin crossed the placenta when administered to rats and that trabectedin should not be used during pregnancy. Section 5.3 was updated with the relevant information of study. The PL was updated accordingly.

	The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IAIN/0046	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/12/2015	29/06/2016	SmPC	
PSUSA/3001/ 201409	Periodic Safety Update EU Single assessment - trabectedin	23/04/2015	19/06/2015	SmPC	Please refer to EMEA/H/C/PSUSA/00003001/201409 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
S/0042	7th Annual Re-assessment	26/03/2015	27/05/2015	SmPC, Annex II 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 Yondelis should be maintained. As all Specific Obligations have been fulfilled, the CHMP considered that there were no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances.
IAIN/0044	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	20/05/2015	n/a		

IAIN/0041	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure	28/11/2014	n/a		
PSUV/0038	Periodic Safety Update	25/04/2014	23/06/2014	SmPC and PL	Update of section 4.5 of the SmPC to add a warning on drug interactions. The Package leaflet is updated accordingly. Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation.
S/0037	Annual re-assessment.	20/03/2014	03/06/2014	Annex II	
IB/0039	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)	06/03/2014	03/06/2014	SmPC	
IA/0040	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	24/02/2014	n/a		
II/0036	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	18/12/2013	n/a		
II/0034	Update of section 4.4. to add a warning on allergic reactions / hypersensitivity and section 4.8 in order to update the safety information on hepatic failure,	27/06/2013	18/12/2013	SmPC, Annex II and PL	The safety information of trabectedin Summary of product characteristics and Package Leaflet has been updated with findings from cumulative analyses assessed within the

	septic shock, allergic reactions and hypersensitivity, and an editorial update of the wording of section 6.6 of the SmPC in order to clarify instructions for the preparation of the infusion. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				periodic safety update report to include the following information: Rare cases of hepatic failure (including cases with fatal outcomes) have been reported in patients with serious underlying medical conditions treated with trabectedin, both in clinical trials and in post marketing setting. Some potential risk factors that may have contributed to increased trabectedin toxicity observed in these cases were dose management inconsistent with recommended guidelines, potential CYP3A4 interaction due to multiple competing CYP3A4 substrates or CYP3A4 inhibitors, or lack of dexamethasone prophylaxis. During clinical trials, hypersensitivity was reported in 2% of patients receiving trabectedin either alone or in combination with PLD, and most of these cases were Grade 1 or 2 in severity. During post marketing experience, hypersensitivity reactions with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with PLD. Cases of septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience, in patients treated either with monotherapy or combination therapy.
IAIN/0035/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	25/04/2013	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
S/0033	5th Annual Re-assessment	21/03/2013	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0029	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	18/12/2013	SmPC	
II/0028	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	18/12/2013	SmPC and PL	
IB/0032	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/12/2012	n/a		
IB/0031	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	10/12/2012	n/a		
IA/0030	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	06/11/2012	n/a		

R/0025	Renewal of the marketing authorisation.	24/05/2012	03/08/2012	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Yondelis continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Yondelis, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted with unlimited validity. The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP. Additional data on the investigation to elucidate whether predictors of response to Yondelis in patients with soft tissue sarcoma can be identified (SOB 001) is awaited.
IB/0027/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/07/2012	n/a		
IAIN/0026/G	This was an application for a group of variations.	10/05/2012	n/a		

	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
S/0024	Annual re-assessment.	19/01/2012	27/02/2012		
II/0022/G	This was an application for a group of variations. The MAH proposed the update of section 5.1 of the SmPC in order to add a statement regarding the absence of effect of trabectedin on QTc interval following the results of a QT/QTc study and to update the overall survival data from the pivotal trial ET743-OVA-301 in the indication of ovarian cancer with the final results as requested by the CHMP within the Follow up measure FUM 019. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template	15/12/2011	31/01/2012	SmPC, Annex II, Labelling and PL	Study (ET743-OVC-1001) was requested by the US FDA and was conducted to assess the potential effects of trabectedin on the QT/QTc interval duration measured by electrocardiograms (ECGs) in subjects with advanced solid tumor malignancies when administered at a therapeutic dose of 1.3 mg/m2. This study showed that trabectedin did not prolong the QTc interval as measured by ECGs in subjects with advanced solid tumor malignancies when administered at a therapeutic dose. The results of this study meet the criteria for a negative QT/QTc study. The safety and pharmacokinetic profile of trabectedin was

	version. The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				similar to that observed in previous studies. No adverse events were reported suggestive of proarrhythmic potential. The final overall survival (OS) data from the pivotal trial ET743-OVA-301 were requested by the CHMP as a Follow Up Measure 019 to a Type II variation for a new indication to use Yondelis in the treatment of patients with relapsed platinum-sensitive ovarian cancer. The updated OS analysis, including 522 events, continues to show a positive trend towards improved survival in the Yondelis + PLD compared to PLD, though this did not reach statistical significance with a hazard ratio of 0.086 and a p-value of 0.0835. When OS analysis was adjusted for pre-specified co-variates and using platinum-free interval as a continuum, the improvement in survival was significant with a Hazard ratio of 0.082 and a p-value of 0.0285.
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	23/11/2011	n/a		
IB/0021	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	08/06/2011	n/a		
S/0019	Annual re-assessment.	17/02/2011	16/05/2011	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.

IA/0018	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/11/2010	n/a		
IA/0017	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	25/10/2010	n/a	Annex II	
IB/0015	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	22/06/2010	n/a		
IB/0014	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	03/06/2010	n/a		
IB/0013/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/06/2010	n/a		

S/0012	Annual re-assessment.	18/02/2010	22/02/2010	SmPC	
II/0008	This type II variation concerns the addition of a new indication of Yondelis in combination with pegylated liposomal doxorubicin (PLD) in the treatment of patients with relapsed platinum-sensitive ovarian cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SPC have been updated. The Package Leaflet has been updated accordingly. Further, annex II has been updated to include the agreed version 6.0 of the RMP. Extension of Indication	24/09/2009	28/10/2009	SmPC, Annex II and PL	The scientific discussion of this report will be published.
IB/0011	IB_17_a_Change in re-test period of the active substance	16/07/2009	n/a		
II/0009	Update of DDPS (Pharmacovigilance)	29/05/2009	23/06/2009	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated with the new version number of the agreed DDPS (version 3.0).
S/0006	1st Annual Reassessment	23/04/2009	22/06/2009	SmPC and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of Yondelis, recommended that amendments of Annexes I, II and IIIB of the Commission Decision are necessary. Further to the review of the post-marketing data during the preparation of this annual re-assessment application, the

					Marketing Authorisation Holder proposed to strengthen the current wording on severe local infusion reactions in sections 4.4 and 4.8 of the SPC and the Package Leaflet and to include the medicinal product aprepitant in the list of CYP3A4 inhibitors, which could potentially interact with trabectedin. The proposed changes were acceptable to the CHMP. Since there is still a specific obligation which needs to be fulfilled, the CHMP recommended that the marketing authorization of Yondelis remains under exceptional circumstances.
II/0010	minor change to the manufacturing process of the active substance Quality changes	29/05/2009	03/06/2009		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	The MAH applied to revise Section 6.6 (Special precautions for disposal and other handling) of the SPC and in the PL to modify the instructions for handling and administration of Yondelis. This change is related to the reduction of volume (from 500ml to 50ml) of diluent in which the reconstituted solution is diluted for administration through a central venous line, and consequently to limit the nominal concentration of trabectedin infusion solution to 30µg/ml. In addition, the MAH wants to add Polyisoprene reservoirs and Type I glass bottles as compatible packaging materials with Yondelis diluted solutions.
N/0005	Minor change in labelling or package leaflet not	03/06/2008	n/a	Labelling	

	connected with the SPC (Art. 61.3 Notification)				
IB/0004	IB_17_a_Change in re-test period of the active substance	16/05/2008	n/a		
IA/0003	IA_13_a_Change in test proc. for active substance - minor change	26/03/2008	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	17/03/2008	n/a	SmPC	
IB/0001	IB_10_Minor change in the manufacturing process of the active substance	05/03/2008	n/a		