Part VI: Summary of risk management plan for Yondelis

Summary of risk management plan for Yondelis (trabectedin)

This is a summary of the Risk Management Plan (RMP) for Yondelis. The RMP details important risks of Yondelis, how these risks can be minimised, and how more information will be obtained about Yondelis's risks and uncertainties (missing information).

Yondelis's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Yondelis should be used.

This summary of the RMP for Yondelis should be read in the context of all information including the assessment report of the evaluation and its plain-language summary, which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Yondelis's RMP.

I. The medicine and what it is used for

Yondelis is authorised for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients (see SmPCs for the full indication).

Yondelis in combination with pegylated liposomal doxorubicin (PLD) is authorised for the treatment of patients with relapsed platinum sensitive ovarian cancer (see SmPC for the full indication).

It contains trabectedin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Yondelis benefits can be found in Yondelis EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis#overview-section.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Yondelis, together with measures to minimise such risks and the proposed studies for learning more about Yondelis's risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation measures***.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

II.A List of important risks and missing information

Important risks of Yondelis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yondelis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risks	Capillary Leak Syndrome (CLS) Injection site reactions
Important Potential Risks	Acute Myeloid Leukaemia/ Myelodysplasia (AML/ MDS) Cardiac Dysfunction Pancreatitis, Lipase and/or Amylase increased
Missing Information	None

II.B Summary of important risks

Important identified risk: Capillary Leak Syndrome (CLS)	
Evidence for linking the risk to the medicine	- PSUR 16 (cut off date 17 September 2019) - Investigator's Brochure v.13 - CLS Expert Report 2016 • A cumulative review of postmarketing and clinical trial cases through 9 December 2014 reporting single or multiple concurrent events potentially associated to CLS by an External Independent Adjudication Committee provided sufficient evidence to consider this event an Adverse drug reaction (ADR) for trabectedin. The search retrieved 102 cases which were independently reviewed by the experts and rated for the likelihood of CLS diagnosis (based on pre-specified diagnostic criteria agreed in consensus by the 3 experts) as well as their causality assessment with trabectedin. Of these 102 cases, 38 cases were deemed not to be CLS, in 48 cases CLS was considered as possible (defined as more information is needed to exclude or confirm diagnosis diagnostic criteria met), in 14 cases CLS was considered probable (defined as very strong clinical suspicion with at least 3 diagnostic criteria met) for which causality was assessed as doubtful in 4 of these cases and at least possible in the remaining 10 cases, and in 2 cases, no conclusion could be drawn. Based on this cumulative review, the Marketing Authorisation Holder decided to update the trabectedin SmPC to include CLS as an ADR with a frequency category (estimated from clinical trials) of uncommon.
Risk factors and risk groups	CLS can be idiopathic (Clarkson's disease) or secondary that is mostly due to malignant hematological diseases, viral infections, and treatments such as chemotherapies and therapeutic growth factors (66).
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC Section 4.8* *SmPC section 4.4. where advice is given on re-assessing serum albumin levels and discontinuing trabectedin if a diagnosis of Capillary Leak Syndrome is confirmed.* *PL section 2 and 4.* **Additional risk minimisation measures:** *None*

Important identified risk: Injection site reaction	
Evidence for linking the risk to the medicine	- PSUR 16 (cut off date 17 September 2019) - Investigator′s Brochure v.13 - Clinical trials (CCDS v.14) • In patients with soft tissue sarcoma, in the integrated clinical trials phase 2 and 3, assigned to the recommended regimen [1.5 mg/m^2, 24 hour infusion every 3 weeks], injection site reactions incidence was of 8.5%. In patients with ovarian cancer, in the integrated phase 3 clinical trials, assigned to combination therapy with trabectedin plus PLD, catheter site inflammation and catheter site pain incidence was of 1.6% and 2.4% respectively. - Clinical trial and postmarketing (CCDS v.14 and SmPC) • During clinical studies and post-marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported. SmPC includes these ADRs as uncommon ADRs.
Risk factors and risk groups	In 1 trial on the use of fosaprepitant, younger age (<50 years), low BMI (<22) were both risk factors for injections site reactions (67). The potential for tissue damage is affected by the factors such as the drug concentration, high vesicant potential of drug and the unfiltered amount, tissue exposure and extravasated zone, repeated use of drugs having the vesicant characteristic. The risk factors affecting the formation of extravasation or making this formation easier involves patient characteristics (e.g. extreme age, patients with fragile veins, sedated or confused patients, etc.), diseases where patients are exposed to repeated treatment infusion requiring indwelling catheters such as cancer patients, issues related to the venous access line (such as peripheral IV particularly in areas such as antecubital fossa, on hand, on foot, wrist, thickness of the IV catheter tip, IV catheter length, placement of central catheter in the region instable to motion, bending or dislocation of the catheter, injection needle on the port not fully accessed, excessive back pressure around the needle, fibrin deposition or thrombosis on the catheter) or issues with the insertion line technique (such as inexperienced staff and insufficient information on the drug management) (68,69).
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Sections 4.4 and 4.8* *SmPC sections 4.2, 4.4 and 6.6 where it is recommended to administer trabectedin through a central venous line.* *PL section 2, 3 and 4.* **Additional risk minimisation measures:** *None*

Important potential risk: Acute Myeloid Leukaemia/ Myelodysplasia (AML/ MDS)	
Evidence for linking the risk to the medicine	- PSUR 16 (cut off date 17 September 2019) - Investigator's Brochure v.13 - Secondary haematological malignancies Adhoc report (23 Sept 2014) • The cumulative analysis identified 28 cases reporting haematolog¬ical malignancies in patients who received trabectedin irrespective of causality. The source distribution of cases was 22 cases from clinical trials and 6 spontaneous cases. Twelve (12) cases out of the 28 reported a fatal outcome, 9 due to AML and 3 due to other causes. • Based on this cumulative review of clinical studies and spontaneous cases, the role of trabectedin in the occurrence of AML/MDS is yet to be determined. The majority of the reported cases adequately documented were heavily confounded, mainly by previous or concomitant chemotherapy or radiotherapy well known to induce secondary malignancies and specifically AML/MDS. Only 1 case was not considered to be confounded.
Risk factors and risk groups	Patients heavily pre-treated with chemotherapy and radiation. Among other cytotoxics, PLD and alkylating agents such as ifosfamide have been associated with an increased risk for secondary AML and MDS. Other risk factors include smoking which can double or triple the risk of AML, genetics, blood disorders such as myelodysplastic syndrome, autoimmune conditions such as rheumatoid arthritis, and being over weight.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section 5.3* **Additional risk minimisation measures:** *None*

Important potential risk: Cardiac Dysfunction	
Evidence for linking the risk to the medicine	- PSUR 16 (cut off date 17 September 2019) - Investigator′s Brochure v.13 - Yondelis SmPC - Cardiac Safety Report (28 Jun 2018) • This report summarizes the cardiac safety data from clinical studies and integrated data analysis sets for subjects with solid tumors who received trabectedin as a monotherapy or in combination with Doxil. The specific clinical studies and integrated safety analysis sets contributing to this report include: Three randomized, open-label, Phase 3 studies (SAR-3007, OVA-301, and OVC-3006). In Study SAR-3007, trabectedin was administered as a monotherapy and in the 2 other studies (OVA-301 and OVC-3006), trabectedin was administered in combination with Doxil; Integrated safety data from 10 Phase 2 studies and 1 Phase 3 study (SAR-3007) in STS and other solid tumors where trabectedin was administered as a monotherapy at a dose of 1.5 mg/m2 once every 3 weeks as a 24-h IV infusion (q3wk; 24-h); Integrated safety data from the 2 Phase 3 ovarian cancer studies (OVA-301 and OVC-3006) where trabectedin was administered in combination with DOXIL. • The analysis confirmed the need for caution when administering trabectedin as monotherapy to patients with risk factors for developing cardiac related TEAEs or myocardial dysfunction (ie, those patients with a Left Ventricular Ejection Fraction (LVEF) <Lower Limit of Normal (LLN), a history of cardiovascular disease or prior cumulative anthracycline dose of ≥300 mg/m2). If, after careful consideration of benefit versus risk, treatment with trabectedin is initiated in patients with risk factors for developing cardiac-related Adverse Events (AEs) or

	myocardial dysfunction, close monitoring for symptoms and signs of myocardial dysfunction, including but not limited to regular LVEF assessments, is strongly recommended. For subjects with a Grade 3 or 4 cardiac AEs or serious cardiac events indicative of cardiomyopathy or for subjects with an LVEF that decreases below the LLN, trabectedin should be discontinued. Additionally, the data suggested that administration of trabectedin concurrently with Doxil is associated with an increased risk for cardiotoxicity compared with Doxil monotherapy
Risk factors and risk groups	Cardiac dysfunction can be inherited or can be caused by viral infections, autoimmune diseases or exposure to toxins and certain medicines. The elderly are particularly at risk with more than 80% of deaths and prevalent cardiac failure cases occuring in patients ≥ 65 years of age in the USA and Europe. Men also have a greater risk of cardiac failure than women. Patient-related risk factors for cancer therapy-related cardiac dysfunction include: those with pre-existing cardiac risk factors such as hypertension, diabetes mellitus, smoking, previous left ventricular dysfunction, heart failure, coronary disease, increasing age, female gender, and postmenopausal sta0tus (70). Additional risk factors for developing heart damage include hypertension, obesity, radiation therapy involving the heart region, exposure to or previous exposure to cyclophosphamide, iphosphamide or amsacrine and existing heart disease. Chemotherapy induced cardiotoxicity often presents as dose-dependent cardiomyopathy that can lead to chronic heart failure. Anthracyclines are recognised to increase the risk of cardiac dysfunction with more than one half of patients exposed to anthracyclines developing some degree of cardiac dysfunction 10 to 20 years after chemotherapy, with 5% developing overt chronic heart failure. (71, 72, 73, 74, 75, 76, 77). In Trial ET743-SAR-3007, Higher CAD, advancing age, abnormal baseline LVEF, and cardiac medical history were identified through a Multi-Variate Analysis (logistic regression) as independent risk factors of LVEF decline.
Risk minimisation measures	**Routine risk minimization measures:** *SmPC Section 4.8* *SmPC section 4.4 where advice is given on monitoring LVEF.* *PL section 2, 3 and 4* **Additional risk minimization measures:** None proposed

Important potential risk: Pancreatitis, Lipase and/or Amylase increased	
Evidence for linking the risk to the medicine	- PSUR 16 (cut off date 17 September 2019) - Investigator′s Brochure v.13 - Yondelis SmPC
Risk factors and risk groups	Concomitant use of drugs described to produce pancreatitis, including ranitidine, paroxetine, celecoxib, and/ or capecitabine,any previous or concomitant biliary tract disease, or gallstones, prior history of cholecystectomy or other biliary or pancreatic surgery, hypercholesterolemia, history of use of ethanol (alcoholism), recent abdominal trauma, pancreatic malignancy, or a family history of pancreatitis.. Risk factors for developing severe acute pancreatitis (with increased mortality) are older age (>55), obesity (Body Mass Index >30), organ failure and pleural effusion and/or infiltrates at admission. Several populations at higher risk have been identified during research in drug-induced pancreatitis. Predisposing demographic characteristics are female gender and younger age. Three types of diseases were recognised as the most frequent predisposing health factors in drug-induced pancreatitis: inflammatory bowel diseases, human immunodeficiency virus (HIV) infection and cancer treated by combined chemotherapy.
Risk minimisation measures	**Routine risk minimization measures:** No risk minimisation measures **Additional risk minimisation measures:** None proposed

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Yondelis.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Yondelis.