Summary Basis of Decision (SBD)

PrYONDELIS™

Trabectedin, 0.25 mg /vial and 1.0 mg/vial, powder for solution
Janssen-Ortho Inc.
Submission Control Number: 124729

Date Issued | 2010/09/23

Health Products and Food Branch
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Health Products and Food Branch

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Numéro de contrôle de la présentation : 124729
FOREWORD

Health Canada’s Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within the evaluation reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the ‘Reader’s Guide to the Summary Basis of Decision - Drugs’ to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled ‘How Drugs are Reviewed in Canada’. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the ‘Summary Basis of Decision Initiative - Frequently Asked Questions’ document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events (AE), interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under ‘Related Links’ on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the ‘Management of Drug Submissions Guidance’.
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1 PRODUCT AND SUBMISSION INFORMATION

Brand Name: PrYONDELIS™
Manufacturer/Sponsor: Janssen-Ortho Inc.
Medicinal Ingredient: Trabectedin
International Non-proprietary Name: Trabectedin
Strengths: 0.25 mg/vial and 1.0 mg/vial
Dosage form: Powder for solution
Route of Administration: Intravenous
Drug Identification Numbers: 02351501 - 0.25 mg/vial
02351528 - 1.0 mg/vial
Therapeutic Classification: Antineoplastic agent
Non-medicinal Ingredients: Phosphoric acid, potassium dihydrogen phosphate, potassium hydroxide, sucrose
Submission Type and Control Number: New Drug Submission,
Control Number: 124729
Date of Submission: 2009/06/01
Date of Authorization: 2010/05/13

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2 NOTICE OF DECISION


Yondelis™ contains the medicinal ingredient trabectedin which is an antineoplastic agent.

Yondelis™ in combination with Caelyx® [pegylated liposomal doxorubicin hydrochloride (PLD)] is indicated for the treatment of patients with platinum-sensitive ovarian cancer for whom one first-line platinum-based chemotherapy regimen, including adjuvant therapy, has failed and who are not expected to benefit, are ineligible or not willing to receive retreatment with platinum-based chemotherapy. Approval of Yondelis™ in combination with Caelyx® is based on progression-free survival (PFS) benefit in patients with relapsed ovarian cancer. A prolongation of overall survival or quality of life benefit has not been demonstrated.

Yondelis™ is a cytotoxic agent which binds to the minor groove of deoxyribonucleic acid (DNA) subsequently bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

The market authorization was based on quality, non-clinical, and clinical information submitted. In support of the proposed indication, a Phase III, open-label, multicentre, randomized study was submitted comparing the combination of Yondelis™ with Caelyx® or Caelyx® alone in subjects with advanced relapsed ovarian cancer. A total of 663 patients with advanced relapsed ovarian cancer whose disease had progressed on or after one first-line platinum-based therapy (including adjuvant therapy) were randomized to one of two treatment groups: combination of Caelyx®, 30 mg/m², administered as a 90-minute intravenous infusion (IV) followed by Yondelis™ 1.1 mg/m², as a 3-hour IV infusion every three weeks; or Caelyx® alone at a dose of 50 mg/m², administered as a 90-minute IV infusion every four weeks. Results indicated that PFS was longer in patients treated with Yondelis™ in combination with Caelyx® than with Caelyx® alone (median PFS was 7.3 months in the combination treatment group versus 5.8 months in the monotherapy treatment group). However, this result was not consistent within subgroups. While in platinum-sensitive patients the PFS was longer in patients treated with Yondelis™ in combination with Caelyx® than in Caelyx® alone (median PFS was 9.2 months in the combination treatment group versus 7.5 months in the monotherapy treatment group), in platinum-resistant patients the PFS was not different between the two treatment groups (median PFS was 4.0 months in the combination treatment group versus 3.7 months in the monotherapy treatment group). A difference between treatment groups in overall survival or quality of life was
not demonstrated. Significant adverse events associated with Yondelis™ treatment included hepatotoxicity, rhabdomyolysis, febrile neutropenia and sepsis, pulmonary embolism, and injection site reactions.

Yondelis™ (0.25 and 1.0 mg/vial, trabectedin) is presented as a powder for solution. Yondelis™ is used in combination with Caelyx® every 3 weeks. Yondelis™ is administered at a dose of 1.1 mg/m² as a 3-hour IV infusion after Caelyx® 30 mg/m², as a 90-minute IV infusion. All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before Yondelis™ infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed. Furthermore, numerous chemistry laboratory values must be met prior to initiating treatment with Yondelis™. Subsequently, these chemistry laboratory values must continue to be assessed prior to the initiation of each cycle of treatment with Yondelis™. Yondelis™ must not be used in patients with elevated bilirubin levels. Dosing guidelines are available in the Product Monograph.

Yondelis™ is contraindicated for patients who are hypersensitive to Yondelis™ (trabectedin) or to any ingredient in the formulation or component of the container. Yondelis™ is also contraindicated for nursing mothers or to patients with an active serious or uncontrolled infection. Yondelis™ should be administered under the conditions stated in the Product Monograph taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Yondelis™ are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Yondelis™ is favourable for the indication stated above.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

Trabectedin, the medicinal ingredient of Yondelis™, is an antineoplastic agent. Trabectedin is a new cytotoxic agent which binds to the minor groove of DNA, triggering a series of events that interfere with the cell cycle, resulting in reduced growth of various types of cancer cells.
Manufacturing Process and Process Controls

Trabectedin is manufactured via a multi-step synthesis. Each step of the manufacturing process is considered to be controlled within acceptable limits:

- The sponsor has provided information on the quality and controls for all materials used in the manufacture of the drug substance.
- The drug substance specifications are found to be satisfactory. Impurity limits meet International Conference on Harmonisation (ICH) requirements.
- The processing steps have been evaluated and the appropriate ranges for process parameters have been established.

Characterization

The structure of trabectedin has been adequately elucidated and the representative spectra have been provided. Physical and chemical properties have been described and are found to be satisfactory.

Impurities and degradation products arising from manufacturing and/or storage were reported and characterized. These products were found to be within ICH-established limits and/or were qualified from batch analysis, and therefore are considered to be acceptable.

Control of Drug Substance

Copies of the analytical methods and, where appropriate, validation reports were provided for all analytical procedures used for release and stability testing of trabectedin. The drug substance specifications, analytical methods, and validation reports are considered acceptable.

Batch analysis results were reviewed and all results comply with the specifications and demonstrate consistent quality of the batches produced.

The drug substance packaging is considered acceptable.

Stability

Based on the long-term, real-time, and accelerated stability data submitted, the proposed retest period and storage conditions for the drug substance were supported and are considered to be satisfactory.
3.1.2 Drug Product

Description and Composition

Yondelis™ is a sterile, lyophilized, white to off-white powder supplied in individually cartoned 25 mL vials containing 1 mg of trabectedin, or 10 mL vials containing 0.25 mg of trabectedin. The non-medicinal ingredients are phosphoric acid, potassium dihydrogen phosphate, potassium hydroxide, and sucrose.

All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations. The compatibility of trabectedin with the excipients is demonstrated by the stability data presented on the proposed commercial formulation.

Pharmaceutical Development

Changes to the manufacturing process and formulation made throughout the pharmaceutical development are considered acceptable upon review.

Manufacturing Process and Process Controls

The manufacturing process uses conventional manufacturing techniques, namely: compounding, sterile filtration, sterile filling, lyophilisation, stoppering, and capping.

The method of manufacturing is considered acceptable and the process is considered adequately controlled within justified limits.

Control of Drug Product

Yondelis™ is tested to verify that its identity, appearance, content uniformity, assay, pH, reconstitution time, particulate matter, sterility, moisture content, bacterial endotoxins, and levels of degradation products are within acceptance criteria. The test specifications and analytical methods are considered acceptable; the shelf-life and the release limits for individual and total degradation products are within acceptable limits.

Copies of the analytical methods and, where appropriate, validation reports were provided and are considered satisfactory for all analytical procedures used for release and stability testing of Yondelis™.
The proposed limits are considered adequately qualified (that is [i.e.] within ICH limits and/or qualified from toxicological studies). Control of the impurities and degradation products is therefore considered acceptable.

**Stability**

Based on the real-time, long-term, and accelerated stability data submitted, the proposed 36-month shelf-life at 2-8°C for Yondelis™ is considered acceptable.

The compatibility of the drug product with the container closure system was demonstrated through compendial testing and stability studies. The container closure system met all validation test acceptance criteria.

### 3.1.3 Facilities and Equipment

The design, operations and controls of the facilities and equipment that are involved in the production of Yondelis™ are considered suitable for the activities and products manufactured.

All of the proposed manufacturing sites comply with the requirements of Division 2 of the *Food and Drug Regulations*.

### 3.1.4 Adventitious Agents Safety Evaluation

Not applicable. The excipients used in the drug product formulation are not from animal or human origin.

### 3.1.5 Conclusion

The Chemistry and Manufacturing information submitted for Yondelis™ has demonstrated that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes.
3.2 Non-clinical Basis for Decision

3.2.1 Pharmacodynamics

Trabectedin has potent antiproliferative effects that are believed to be based on a unique binding to the minor groove of DNA, bending the helix to the major groove. While the exact mechanism is unknown, the binding of trabectedin to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

*In vitro*, trabectedin exerted potent cytotoxic effects, particularly after prolonged exposures (24-96 hours). Human sarcoma cell lines were particularly sensitive with IC<sub>50</sub> values (concentrations required to inhibit effects by 50%) between 0.0002 to 1.5 nM. Trabectedin also exerted antiproliferative effects in the sub- to low-nanomolar range in a large panel of human carcinoma cells, including ovarian carcinomas (IC<sub>50</sub> 0.13 to 30 nM), and in cell lines resistant to other chemotherapeutic agents such as cis-platinum and paclitaxel after 3 to 5 day incubations.

*In vivo*, trabectedin showed antitumour activity in several tumour grafts of rodent and human origin that included tumour types both sensitive and poorly responsive to other chemotherapeutic agents. Significant inhibition of tumour growth was seen in ovarian, sarcoma, melanoma, non-small cell lung, medulloblastoma, and breast cancer models. Optimal activity was usually obtained at or close to the maximum tolerated dose (MTD) of 300 or 600 µg/m<sup>2</sup>. Higher doses given less frequently appeared more effective than repeated administration of lower doses.

Additive or synergistic effects were seen *in vitro* when trabectedin was combined with doxorubicin or cisplatin in several cell lines but the combination study with doxorubicin has not been carried out with ovarian cells.

Trabectedin induced concentration-dependent myelotoxicity in haematopoietic progenitor cells that were comparable to those of murine and human origin (IC<sub>50</sub> = 15 nM).

In safety pharmacology studies, slow intravenous (IV) bolus trabectedin doses up to 300 µg/m<sup>2</sup> did not cause any neurofunctional effects in rats, consistent with low distribution to the brain. Trabectedin was not cardiotoxic to neonatal rat hearts *in vitro* at concentrations up to 10.0 µg/mL. A slight (approximately 10%) decrease in human Ether-à-go-go Related Gene (hERG) mediated current was only seen at the highest concentration (10<sup>-7</sup> M). Decreases in mean systolic and diastolic arterial blood pressure
occurred in a monkey cardiovascular study, however there were no other cardiovascular effects reported in that study or in subsequent toxicology studies in dogs and monkeys. Therefore, the risk of cardiovascular effects with the use of trabectedin appears low.

### 3.2.2 Pharmacokinetics

**Absorption**

Following IV dosing in mice, rats, dogs, and monkeys, trabectedin demonstrated multi-compartmental kinetics. Exposure was generally dose-proportional, and was independent of time and infusion duration (3 or 24 hours) in rats and monkeys.

**Distribution**

The estimated systemic clearances were moderate to high compared to the respective hepatic blood flows and the apparent volume of distribution values at steady-state were very large, indicative of extensive tissue distribution.

After a single IV bolus dose of radiolabelled trabectedin in male rats, the highest levels of radioactivity occurred in the spleen, lung, adrenal and pituitary glands, lymph nodes, bone marrow, and kidney. Distribution to testicular tissue and especially to the brain was very limited.

Trabectedin was highly bound to plasma proteins in all species tested as well as humans (97%). In an *in vitro* evaluation of the potential for human plasma protein binding interactions with 14 prototypical drugs, none of the drugs at clinically relevant concentrations impacted the protein binding of trabectedin to a significant degree. However, a slight increase (28%) in the free fraction of trabectedin occurred with the highest tested concentrations of phenytoin (400 µM). This suggests that while the potential for displacement of trabectedin from plasma protein binding sites is low, it may be possible at high concentrations of a highly-bound drug such as phenytoin.

*In vitro* studies show that trabectedin is a substrate for P-glycoprotein (P-gp). Inhibitors of P-gp may alter trabectedin tissue distribution.

**Metabolism**

Trabectedin was extensively metabolized in all of the species tested. The metabolic profile for humans was more similar to monkeys compared to rodents and dogs. Most major cytochrome P450 (CYP) enzymes were able to metabolize trabectedin, however
the inhibition studies indicated that CYP3A4 is the main CYP isoform involved at the therapeutically relevant concentration of 10 ng/mL.

Trabectedin was not an inducer of most of the relevant CYP isoforms in cultured human hepatocytes, with mild induction of messenger ribonucleic acid (mRNA) expression evident only at 5 and 10 nM for CYP1A1 and at 1 nM for CYP2C19.

*In vitro*, trabectedin did not inhibit major human recombinant CYP isoforms (1A1, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5) at levels up to 50 nM.

In cultured human hepatocytes, concentration-dependent inhibition of the gene expression of many CYP isoforms occurred mainly at 5 and 10 nM; however, these concentrations were cytotoxic.

**Excretion**

In mice and rats, trabectedin and/or its metabolites were eliminated mainly in the faeces via biliary excretion with only small amounts excreted in urine.

### 3.2.3 Toxicology

**Single and Repeat-Dose Toxicity**

Trabectedin single- and repeat-dose IV toxicology studies generally showed a consistent pattern of effects that were generally comparable, but showed some differences with potential implications for patients. Single doses were given as bolus injections in mice, rats, dogs, and monkeys, as well as 3- and 24-hour infusions in rats. Repeated-dose regimens consisted of 5 consecutive daily bolus injections in mice, rats, and dogs, 1-3 cycles of bolus injections given once every 3 weeks to rats, and 3 cycles of 3 hour infusions given once every 3 weeks to rats. In monkeys, 4 cycles of a 3- or 24-hour infusion every 3 weeks and 3 cycles of an infusion given weekly for 3 weeks/cycle (9 doses total), and 8 cycles of a 3-hour infusion every 3 weeks were evaluated.

All toxicities in all species, including mortality that occurred in most studies, were seen at dose levels that are less than the human therapeutic dose of 1.1 mg/m² when expressed in terms of body surface area for comparison.

Principal toxicities and target organs consisted of the injection site, liver, bone marrow/haematopoietic system, gastrointestinal system, and kidney and to a lesser extent the pancreas, and possibly the eye and teeth.
Injection site lesions were seen in all species at most dose levels. The lesions were generally not reversible or poorly reversible, and were frequently the cause of death or moribund euthanasia in rats and monkeys. However, injection site lesions were generally less apparent in dogs compared to the smaller species tested, indicating that trabectedin would likely have a better local tolerance in humans who have larger blood vessels for infusion.

Hepatobiliary toxicity was observed in all species at relatively low doses, although monkeys were less affected than rodents and dogs. In rats and dogs, increases in transaminase and alkaline phosphatase activities, bilirubin, and bile acid concentrations generally correlated well with the microscopic findings indicating the former to be good biomarkers for hepatobiliary toxicity.

Myelosuppression occurred in all species and was characterized by decreases in red blood cell (RBC) parameters, leucopaenia, neutropaenia, hypocellularity in the bone marrow, and atrophy or depletion of the lymphoid tissues; it was considered the cause of some of the deaths and moribund sacrificed rats and monkeys. Maximal suppression occurred at non-lethal doses between 7 and 10 days post-dose in monkeys. Full or partial reversibility was observed within 3 weeks. Reduced RBC parameters were also frequently observed and considered cumulative in monkeys. Routine haematology appeared to be sufficient to monitor potential haematopoietic toxicity.

Gastrointestinal pathology was observed in all species. It may be related in part to the antiproliferative effects; however, in monkeys, gastrointestinal inflammation and necrosis leading to peritonitis was considered to be due to systemic bacterial infections. This may have been secondary to profound neutropaenia resulting from myelosuppression.

Renal lesions were noted in a few animals in all of the repeat-dose monkey studies; however, they were all considered secondary to severe thrombophlebitis noted in the cannulated vein.

Minor reversible pancreatic lesions were inconsistent and seen in one of the rat studies (minimal acinar cell necrosis), two of the dog studies (acinar cell atrophy/apoptosis or oedema), and one of the monkey studies (minor acinar degranulation) and are not considered a significant concern.

Focal areas of retinal oedema were seen during ophthalmic exams in two (low- and mid-dose) monkeys in one of the studies. This oedema may have been treatment-related, however, a relationship to trabectedin is uncertain given the low incidence and since it was not seen at higher doses or in other monkey studies or other species.
Degeneration of the pulpa matrix of incisors was only seen in wild-type and P-gp-knockout mice.

**Genotoxicity**

Trabectedin was genotoxic in a bacterial mutagenicity (Ames) assay, in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, and in an *in vivo* mouse micronucleus test.

**Carcinogenicity**

Long-term carcinogenicity studies were not performed.

**Reproductive and Developmental Toxicity**

Trabectedin was not embryotoxic or teratogenic in the developmental toxicity studies in rats or rabbits. However, since the doses used were much lower than the human clinical dose, due to dose-limiting maternal toxicity, the results of these studies have little relevance to humans.

No fertility and early development studies were conducted. The cytotoxic and mutagenic properties of trabectedin indicate it is likely to affect reproductive capacity and consequently appropriate precautions need to be taken.

**Local Tolerance**

Local tolerance studies in rabbits confirmed the high irritation potential of trabectedin.

**3.2.4 Conclusion**

In view of the intended use of Yondelis™, there are no pharmacological/toxicological issues within the submission which preclude the approval of its use for the proposed indication. Appropriate warnings and precautionary measures are in place in the Product Monograph to address the identified safety concerns.
3.3 Clinical Basis for Decision

3.3.1 Pharmacodynamics

Two pharmacokinetic (PK)/pharmacodynamic (PD) reports explored the relationships between toxicity-related responses and systemic exposure to Yondelis™. PK and PD modelling were used to characterize the elevation of serum transaminases (serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and bilirubin concentrations in the liver toxicity PK/PD report. Release of ALT and AST from the hepatocyte cytoplasm to the serum is indicative of hepatocyte injury. High bilirubin levels are also an indicator of liver damage. The relationship between trabectedin and neutropaenia were also analyzed in the PK/PD report related to blood dyscrasia.

The studies indicated that treatment with Yondelis™ resulted in the transient elevation of ALT. Results also showed an association between the incidence of total bilirubin toxicity grade ≥2 and the trabectedin exposure parameters (area under the curve [AUC] and maximum plasma concentration [C_{max}]), and dosing schedule. Neutrophil counts also decreased as a result of Yondelis™ administration. The severity of neutropaenia was related to the dose amount and frequency.

A study evaluating the potential effects of a single-dose administration of trabectedin on the QT interval has been completed and Health Canada will be evaluating the study results when the assessment is available. The sponsor has been requested to provide to Health Canada the final results of the QT study as a post-marketing commitment.

3.3.2 Pharmacokinetics

Absorption

The concentration-time profiles of trabectedin in plasma are best characterized by a four-compartment population PK model with linear elimination from the central compartment. Dose proportionality was observed with the plasma C_{max} and AUC values of trabectedin for doses 0.02 to 1.8 mg/mg² administered as 3- and 24-hour infusions. The half-life of this drug in plasma after a 3-hour IV infusion was relatively long with an alpha phase (distribution half-life) of approximately 0.2 hours followed by two protracted phases with half-lives of approximately 6 hours (beta phase) and 175 hours. Little or no accumulation of this drug was observed or expected in the plasma upon repeat administration at 3-week intervals.
Distribution

Trabectedin was extensively bound to plasma proteins \textit{in vitro}, binding more frequently to alpha-1 acid glycoprotein than to albumin.

The large volume of distribution (>5000 L) at steady-state indicates that trabectedin was extensively distributed into the peripheral tissues.

Metabolism

Trabectedin was extensively metabolized in the liver. CYP3A4 was the predominate CYP isozyme responsible for its biotransformation at clinically relevant concentrations.

The pharmacologically active metabolite N-desmethyl-trabectedin was below the limit of detection in human plasma, despite being seen \textit{in vitro}.

Excretion

Following the administration of radiolabelled trabectedin, the majority of the radioactivity (57.6\% of the dose) was excreted in the faeces and much less (5.8\% of the dose) was recovered in the urine. Negligible quantities of unchanged drug were recovered in the urine and faeces, confirming the extensive metabolism of the drug \textit{in vivo}.

Based on the population estimate of the plasma clearance and blood/plasma ratio, the clearance of trabectedin in whole blood is approximately 35 L/hour.

Drug Interactions

Since trabectedin is mainly metabolized by CYP3A4, the concentrations of the drug in the plasma are likely to be affected in patients who are co-administered drugs which are known to induce or inhibit the activity of CYP3A4. No formal clinical studies were conducted to investigate the affect of CYP3A4 inducers and inhibitors on the PK of trabectedin. Co-administration of potent inhibitors of CYP3A4 is not recommended.

Co-administration of Yondelis™ with liposomal doxorubicin may result in a decreased plasma clearance of trabectedin. Data from a Phase III study and a Phase I study showed decreases of 31\% and 16\%, respectively.
Special Populations

Hepatic Impairment

Yondelis™ must not be used in patients with elevated bilirubin levels. The effects of hepatic impairment on the PK of trabectedin have not been adequately studied. Given that trabectedin is metabolized by the liver and is associated with hepatotoxicity, the use of Yondelis™ in patients with clinically relevant liver diseases, such as active chronic hepatitis, is not recommended.

Renal Impairment

Only a minor fraction of the total dose of trabectedin was excreted in the urine as unchanged drug or derived metabolites, therefore the effects of renal impairment on the PK of trabectedin was not formally investigated. However, due to the fact that the studies were not conducted with patients having a creatinine clearance of <60 mL/min, Yondelis™ must not be used in this population.

3.3.3 Clinical Efficacy

The clinical efficacy of Yondelis™ was primarily assessed in one pivotal, open-label, active control, multicentre, randomized Phase III study comparing the combination of Caelyx® (pegylated liposomal doxorubicin hydrochloride) 30 mg/m², administered as a 90-minute IV infusion followed by Yondelis™ 1.1 mg/m² as a 3-hour IV infusion, every 3 weeks; with Caelyx® alone at a dose of 50 mg/m² administered as a 90-minute IV infusion every 4 weeks. A total of 672 patients who had been treated previously for advanced ovarian cancer, and for whom a first-line platinum-based chemotherapy regimen had failed were randomized for treatment.

At the time of randomization, patients were stratified on the basis of platinum sensitivity of disease (sensitive or resistant) and baseline Eastern Cooperative Oncology Group (ECOG) performance status score. Platinum-sensitive patients were patients who progressed more than 6 months after the end of first-line platinum-based treatment. Platinum-resistant patients were patients who progressed earlier then 6 months after the end of treatment.

Treatment continued until disease progression occurred or for at least two cycles after a confirmed complete response. The primary endpoint was originally specified as overall survival (OS) but was changed, following a protocol amendment, to progression-free survival (PFS) based on assessments by independent radiologists (which excluded
assessments of clinical data). Additional analyses were done based on assessments by independent oncologists and the study investigators. The analysis of the primary efficacy endpoint (PFS) was to be conducted after 415 events of disease progression or death occurred. An interim analysis of one of the secondary endpoints, OS, was conducted in conjunction with PFS at 300 deaths. The study was to end 2 months after the last patient received the last dose of study medication or after 520 deaths were observed, whichever was later. An ad-hoc OS analysis was also conducted at 419 deaths. Other secondary endpoints included objective response rate (ORR) and quality of life (QOL).

According to the independent radiologist assessments, treatment with Yondelis™ + Caelyx® resulted in a 21% risk reduction for disease progression compared to Caelyx® monotherapy. The median PFS was 7.3 months for those who were treated with Yondelis™ + Caelyx® compared to 5.8 months for those who were treated with Caelyx® alone. The proportion of progression-free patients at 12 months in the Caelyx® monotherapy arm was 18.5% compared to 25.8% in the Yondelis™ + Caelyx® arm.

In a second analysis of PFS based on assessments conducted by the independent oncologists, treatment with Yondelis™ + Caelyx® resulted in a 28% risk reduction for disease progression compared to Caelyx® monotherapy. The median PFS was 7.4 months for those that were treated with Yondelis™ + Caelyx® compared to 5.6 months for those that were treated with Caelyx® alone. The proportion of progression-free patients at 12 months in the Caelyx® monotherapy arm was 16.2% compared to 26% in the Yondelis™ + Caelyx® arm.

In a third analysis of PFS based on assessments conducted by investigators, the Yondelis™ + Caelyx® arm resulted in a 28% risk reduction for disease progression. The median PFS was 5.6 months for Caelyx® monotherapy and 7.4 months for Yondelis™ + Caelyx®.

Analysis of the PFS results shows that, although there were some discrepancies between the assessments of independent radiologists, oncologists, and investigators, the observed improvement of PFS in the Yondelis + Caelyx® arm was robust, as evidenced by the consistency of the results of the PFS analyses whether based on independent radiologists', independent oncologists' or investigators' assessments.

Further analysis of PFS within subgroups based on platinum-sensitivity suggest that Yondelis™ may not be effective in platinum-resistant patients. For the platinum-sensitive patients, the median PFS was 9.2 months for those that were treated with Yondelis™ + Caelyx® and 7.5 months for those who were treated with Caelyx® alone. For platinum-resistant patients, the PFS was not significantly different between the two
treatment groups. The median PFS was 4.0 months for the Yondelis™ + Caelyx® group versus (vs.) 3.7 months for the Caelyx® group. Similar results for objective response rate (ORR) by platinum sensitivity were observed from the integrated three non-pivotal Phase II supportive studies using Yondelis™ alone. The ORR was higher in patients with platinum-sensitive disease than in patients with platinum-resistant disease.

Two interim analyses of OS were performed; one after 300 deaths, and another after 419 deaths. After 300 deaths, the median OS was 19.4 months in the Caelyx® arm and 20.5 months in the Yondelis™ + Caelyx® arm; the difference was 1.1 month. After 419 deaths, the median OS was 19.5 months in the Caelyx® arm and 22.4 months in the Yondelis™ + Caelyx® arm. The difference between the two study arms was 2.9 months. The results show a trend toward an improvement in OS in the Yondelis™ + Caelyx® arm, but the difference was not statistically significant. In both analyses, the trend toward improved OS was greater in the platinum-sensitive patients. The final analysis will be performed after 520 deaths and the report is expected in 2011. The sponsor was requested to provide to Health Canada the final OS analysis as a post-marketing commitment.

The ORR was significantly higher in the Yondelis™ + Caelyx® arm (27.6%) compared to the Caelyx® arm (18.8%). In the subgroup of patients who were platinum-resistant, there was no significant difference between the two treatment arms. The ORR based on investigator tumour assessments in the subgroup of patients with platinum-sensitive disease in the Yondelis™ + Caelyx® treatment arm was higher than ORRs reported in the Phase II single-arm studies of Yondelis monotherapy for patients with platinum-sensitive ovarian cancer.

No statistically significant differences were found between treatment arms in global measures of QOL.

### 3.3.4 Clinical Safety

The clinical safety evaluation of Yondelis™ was based on the safety data obtained from the Phase III pivotal study, the 19 completed Phase II studies, and all of the serious adverse drug reactions from the Phase I studies, the outgoing studies, and the post-market database.

The pivotal study included 663 patients with advanced relapsed ovarian cancer who received either Caelyx® (30 mg/m²) followed by Yondelis™ (1.1 mg/m²) every 3 weeks or Caelyx® alone (50 mg/m²) every 4 weeks. The combination of Yondelis™ + Caelyx® was given to 333 patients. In this combination arm, the median number of cycles given was 6.0 cycles (range: 1 to 21) for a median of 19 weeks. In the Caelyx® arm, the median
The number of cycles given was 5.0 cycles (range: 1 to 22) for a median of 20 weeks. The following paragraphs contain data from the pivotal study unless otherwise noted.

The number of treatment-emergent adverse events (TEAEs) was high in both treatment groups; however, the percentages of total drug-related adverse events (AEs), Grade 3-4 AEs, serious adverse events (SAEs) and AEs leading to treatment termination were higher in the Yondelis™ + Caelyx® arm compared to the Caelyx® arm.

The most common AEs were gastrointestinal (GI) disorders (83% in Caelyx® arm and 89% in the Yondelis™ + Caelyx® arm). While the overall incidence was similar in both arms, the frequencies for certain events differed by more than 10%, for example (e.g.) nausea (42% vs. 74%), and vomiting (30% vs. 56%) for the Caelyx® arm and the Yondelis™ + Caelyx® arm, respectively. In addition, the severity was greater in the Yondelis™ + Caelyx® arm. Of all the GI disorders, 16.7% of the patients had Grade 3-4 toxicity in the Caelyx® arm and 20.9% had Grade 3-4 toxicity in the Yondelis™ + Caelyx® arm. Nausea was experienced by 6.5% vs. 12.2%, and vomiting was experience by 8.9% vs. 19.8%, for the Caelyx® arm and the Yondelis™ + Caelyx® arm, respectively.

The most common AEs, reported in ≥20% of the patients in the Yondelis™ + Caelyx® arm were neutropaenia, leukopaenia, anaemia, thrombocytopaenia, nausea, vomiting, diarrhoea, hand-foot syndrome, fatigue, increased ALT, increased AST, increased blood alkaline phosphatase, constipation, abdominal pain, and stomatitis.

The number of patients with SAEs was greater in the Yondelis™ + Caelyx® arm (39% vs. 31%) with significant prevalence of blood and lymphatic system disorders (such as neutropaenia, thrombocytopaenia, anaemia) and vomiting. The toxicity grade was also higher in the Yondelis™ + Caelyx® arm compared to the Caelyx® arm.

The following safety topics were identified for special consideration concerning the use of Yondelis™ in combination with Caelyx® because of their potential for clinical importance:

- Hepatic toxicity;
- Haematological toxicity (neutropaenia, febrile neutropaenia and infection, thrombocytopaenia and bleeding events);
- Abdominal pain;
- Creatine phosphokinase (CPK) elevation and rhabdomyolysis;
- Cardiotoxicity;
• Renal and urinary disorders;
• Extravasation (injection site reaction);
• Respiratory disorders including pulmonary embolism;
• Myelodysplasia and AML;
• Other events - ototoxicity, neuropathy, and hypersensitivity.

**Hepatic Toxicity**

In the pivotal study, the incidence of ALT Grade 3 or 4 toxicity was 1% in the Caelyx® arm and 31% in the Yondelis™ + Caelyx® arm. Three patients (0.9%) in the Yondelis™ + Caelyx® arm experienced abnormalities that fulfill the criteria for Hy’s law for predicting severe liver toxicity; however, all liver toxicity was resolved by dose reduction or cycle delay. Even though there were significant increases in liver transaminases, all of the cases were manageable and reversible. The combination of elevated levels of ALT, AST, and blood alkaline phosphatase was the most frequent hepatobiliary-related AE. Few cases of hepatotoxicity were reported.

**Haematological Toxicity**

The incidence of Grades 3 and 4 AEs for neutropenia was higher in the Yondelis™ + Caelyx® arm (63%) compared with the Caelyx® arm (22%). In the Yondelis™ + Caelyx® arm, 8% of the patients developed Grade 3-4 neutropenic fever compared with 2% in the Caelyx® arm. Two patients in the Yondelis™ + Caelyx® arm developed neutropenic sepsis and 1 patient experienced sepsis. Neutropenia was managed by dose delays, dose reductions, as well as the use of colony stimulating agents. In the pivotal study, there were 3 cases of death due to SAEs, all of them were caused by neutropenia and its complications (sepsis and febrile neutropenia).

Grade 3 or 4 abnormalities in platelet counts were observed for 77 patients (23%) in the Yondelis™ + Caelyx® arm compared to 14 patients (4%) in the Caelyx® arm. However, the percentages of patients who experienced bleeding-related AEs were similar in both treatment groups.

**Abdominal Pain**

A similar number of patients had abdominal pain between the two treatment arms: 27% in the Yondelis™ + Caelyx® arm and 30% in the Caelyx® arm. The percentage of patients who experienced Grade 3-4 events was higher in the Yondelis™ + Caelyx® arm (5% vs. 1%).
CPK Elevation and Rhabdomyolysis

Rhabdomyolysis and/or elevations in creatine phosphokinase (CPK) in the early Phase II studies were associated with death in 3 patients, commonly as a component of a syndrome that included neutropaenia, sepsis, renal failure and elevated liver enzymes. Thereafter, strict monitoring of liver function and CPK levels and dose adjustment guidelines were implemented in all future and ongoing clinical studies, including the pivotal study. Severe CPK elevations were observed in 2% of patients treated with Yondelis™ in combination with Caelyx®.

Cardiotoxicity

The percentage of Grade 2 or greater cardiac-related AEs was higher in the Yondelis™ + Caelyx® arm (3%) compared to the Caelyx® arm (2%). The most common cardiac AE in the Yondelis™ + Caelyx® arm was congestive heart failure (2%). One case of QT prolongation was also reported.

Renal and Urinary Disorders

Renal and urinary disorder-related AEs consisted mainly of laboratory abnormalities, such as increased levels of blood creatinine and blood urea. Five patients (2%) in the Yondelis™ + Caelyx® arm experienced renal failure.

Extravasation

Administration through a central venous line is required. One percent of patients in the Yondelis™ + Caelyx® arm and 4 to 6% of patients in the Phase II studies experienced extravasation-related AEs. In the Yondelis™ + Caelyx® arm, one patient experienced Grade 3 extravasation resulting in treatment discontinuation.

The percentages of catheter-related adverse drug reactions were 14% and 3% in the Yondelis™ + Caelyx® arm and the Caelyx® arm, respectively.

Respiratory Disorders including Pulmonary Embolism

There were 17 (5%) and 8 (2%) cases of pulmonary embolism reported in the Yondelis™ + Caelyx® arm, and in the Caelyx® arm, respectively. In the integrated Phase II safety analysis set there were no reports of pulmonary embolism; however, 8 subjects (0.8%) experienced drug-related events including dyspnoea, hypoxia and pulmonary hypertension.
Myelodysplasia and Acute Myeloid Leukemia

There were no reports of myelodysplasia in the completed Phase II or Phase III, but there are 3 reports in the ongoing studies.

Acute myeloid leukemia (AML) was found in 2 patients in the Phase II studies (one after 3 trabectedin cycles and the second after 12 cycles). Both patients died.

In the pivotal study, there were no reports of AML during the study. One of the patients died 99 days after the last dose and the causes of death were neutropaenia, pneumonia and AML. A second patient was diagnosed 95 days after the last dose of study drug. He died 3 months and 12 days after due to disease progression.

Other Events – Ototoxicity, Neurotoxicity, and Hypersensitivity

Ototoxicity - Deafness was reported in 3 patients in the Yondelis™ + Caelyx® arm and in 1 patient in the Caelyx® arm. While the deafness was reported to be persisting in all 4 cases, it did not result in treatment discontinuation.

Neurotoxicity - Neurotoxicity-related AEs consisted of peripheral sensory neuropathy, reported for 5% of patients in the Yondelis™ + Caelyx® arm, and 3% of patients in the Caelyx® arm; peripheral neuropathy, reported for 3% of patients in the Yondelis™ + Caelyx® arm and 2% in the Caelyx® arm; and neurotoxicity not otherwise specified, reported for 3 patients (1%) in each treatment arm. None of these neurotoxicity events led to cycle delay or dose reduction, while 1 led to treatment discontinuation in patient in the Yondelis™ + Caelyx® arm.

Hypersensitivity - Hypersensitivity was reported in 2% of patients receiving Yondelis™ either alone or in combination with Caelyx®, and most of these cases were grade 1 or 2 in severity. In the pivotal study, the number of hypersensitivity-related AEs was lower in the Yondelis™ + Caelyx® arm compared with the Caelyx® arm. Greater than 98% of subjects in the Yondelis™ + Caelyx® arm received dexamethasone premedication prior to Yondelis™ administration.
3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

Canadian clinical experts were consulted during the assessment of the clinical efficacy and safety of Yondelis™. The advice received was taken into account in the final conclusions and decisions made by Health Canada.

In a Phase III randomized clinical study, Yondelis™ in combination with Caelyx® demonstrated a small (~6 weeks difference in medians), but significant improvement in PFS and a higher ORR compared to Caelyx® therapy alone for patients with advanced ovarian cancer whose disease had progressed on or after platinum-based therapy (including adjuvant therapy). However, no improvement in OS or QOL was demonstrated, and the PFS and ORR results were not consistent within subgroups based on platinum-sensitivity. Patients with platinum-resistant disease showed no improvement in PFS or ORR. Furthermore, current Canadian guidelines recommend retreatment with platinum-based chemotherapy in patients with recurrent platinum-sensitive ovarian cancer, providing there are no contraindications. As the combination of Yondelis™ and Caelyx® in comparison to a platinum-based regimen has not been studied, and inclusion criteria limited the study population to patients who were not candidates for platinum retreatment, the demonstrated benefit is considered to be limited to patients who have platinum-sensitive recurrent disease and are not candidates for retreatment with a platinum regimen.

The safety analysis showed that almost all Yondelis™-treated patients experienced drug-related AEs, and 89% experienced Grade 3-4 AEs. The most common AEs were increased levels of ALT and AST. Grade 3 or 4 neutropenia was also commonly reported and associated with Yondelis™ combination therapy with Caelyx®. Neutropenia was sometimes associated with complications such as febrile neutropenia, sepsis and infections, some of which were fatal. Other significant AEs were: hepatotoxicity, CPK elevation/rhabdomyolysis, pulmonary embolism, and injection site reactions such as extravasation and necrosis. Although the frequencies of AEs were high and their severity significant, the drug-related AEs are considered generally manageable. The safety concerns can be addressed by careful monitoring, secondary treatments (including premedication with dexamethasone), dose interruptions, discontinuations where necessary, and administration of Yondelis™ through a central line.
The risk management plan for Yondelis™ was requested by Health Canada and provided by the sponsor. All of the potential risks, risk management strategies, and laboratory criteria required to allow treatment with Yondelis™ were discussed and addressed in the plan. Yondelis™ must not be used in patients with elevated bilirubin levels. Premedication with dexamethasone is required not only for prevention of nausea and vomiting but also for the prevention of liver toxicity. In case of neutropaenia, treatment with colony-stimulating growth factors may be beneficial.

Prior to each treatment cycle, patients must fulfill the following criteria:

- Absolute neutrophil count $\geq 1,500/\text{mm}^3$;
- Platelet count $\geq 100,000/\text{mm}^3$;
- Haemoglobin $\geq 9 \text{ g/dL}$;
- Bilirubin $\leq$ upper limit of normal (ULN);
- Alkaline phosphatase of non-osseous origin $\leq 2.5 \times \text{ULN}$ [consider hepatic isoenzymes 5 nucleotidase or gamma-glutamyl transpeptidase (GGT), to distinguish if the elevation could be osseous in origin];
- Albumin $\geq 25 \text{ g/L}$;
- ALT and AST $\leq 2.5 \times \text{ULN}$;
- Serum creatinine $\leq 1.5 \text{ mg/dL}$ ($\leq 132.6 \mu\text{mol/L}$) or creatinine clearance $\geq 60 \text{ mL/min}$;
- CPK $\leq 2.5 \text{ ULN}$.

A Serious Warnings and Precautions Box has been included in the Product Monograph highlighting hepatotoxicity, rhabdomyolysis/severe CPK elevation, febrile neutropaenia, sepsis, pulmonary embolism, injection site reactions, and the proscription in patients with elevated bilirubin levels.

Despite the inability to show an improvement in OS or effectiveness in platinum-resistant patients and the relatively small improvement in PFS, Yondelis™ in combination with Caelyx® is likely to provide a clinically meaningful benefit to platinum-sensitive patients with relapsed ovarian cancer who have progressed after initial treatment with platinum-based therapies and are not expected to benefit, ineligible or not willing to receive treatment with platinum-based therapy. Based on the totality of the data, and an unmet medical need in patients who are not candidates for retreatment with a platinum-based regimen, Health Canada considers that the potential benefit of Yondelis™ outweighs the associated risks for this patient population.
3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Yondelis™ in combination with Caelyx® is favourable for the treatment of patients with platinum-sensitive ovarian cancer for whom one first-line platinum-based chemotherapy regimen, including adjuvant therapy, has failed and who are not expected to benefit, are ineligible or not willing to receive retreatment with platinum-based chemotherapy. The New Drug Submission complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the Food and Drug Regulations.

4 SUBMISSION MILESTONES

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