הודעה על החמרה (מידע בטיחות) בעלון לצרכן

תאריך: 17.1.16

שם תכשיר באנגלית: Yondelis 1mg

מספר רישום: 142 85 31830 00

שם בעל הרישום: J-C Health care

הודעה על החמרה (מידע בטיחות) בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Duration of treatment In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. Yondelis has been administered for 6 or more cycles in 29.5% of patients. The monotherapy regimen has been used for up to 38 cycles. No cumulative toxicities have been observed in patients treated with multiple cycles.		**Posology and method of administration**
Neutropenia, and thrombocytopenia ~~and leucopenia~~ Grades 3 or 4 neutropenia and thrombocytopenia associated with Yondelis therapy have been very commonly reported.	Neutropenia, thrombocytopenia and leucopenia Grades 3 or 4 neutropenia and thrombocytopenia associated with Yondelis therapy have been very	**warnings and precautions**

~~Neutrophil nadirs occurred at a median of 15 days and recovered within a week.~~ A full blood cell count including differential and platelet count must be performed at baseline, weekly for the first two cycles and then once between cycles (see *Dosage and Administration*). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately. This medicine contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially "potassium-free".	commonly reported. Neutrophil nadirs occurred at a median of 15 days and recovered within a week. A full blood cell count including differential and platelet count must be performed at baseline, weekly for the first two cycles and then once between cycles (see *Dosage and Administration*). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately.	
~~Effects of other substances on trabectedin~~ ~~Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not.~~ ~~Since trabectedin is metabolized mainly by CYP3A4, the metabolic clearance of trabectedin is likely to be decreased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CYP3A4 may increase the metabolic clearance of trabectedin.~~ ~~Two drug-drug interaction Phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampin,~~	Effects of other substances on trabectedin Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration relative to those who did not. Since trabectedin is metabolized mainly by CYP3A4, the metabolic clearance of trabectedin is likely to be decreased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CYP3A4 may increase the metabolic clearance of trabectedin. Two drug-drug interaction Phase 1 studies have confirmed trends toward increased and decreased trabectedin	**Interaction with other medicinal products and other forms of interaction**

~~respectively.~~ ~~In a drug-drug interaction study (n=8) with ketoconazole, a potent CYP3A4 inhibitor, systemic exposure of trabectedin was increased by approximately 21% (C_{max}) and 66% (AUC_{last}), when trabectedin was given concomitantly with ketoconazole (total daily dose of 400 mg). Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see Dosage and Administration).~~[ii] ~~In a drug-drug interaction study (n=8) with rifampin, a potent CYP3A4 inducer, systemic exposure of trabectedin was decreased by approximately 22% (C_{max}) and 31% (AUC_{last}), when trabectedin was given concomitantly with rifampin (total daily dose of 600 mg). Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampin, phenorbarbital, Saint John's Wort) should be avoided if possible.~~ ~~Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product (see section 4.4).~~ ~~Preclinical data have demonstrated that trabectedin is a substrate to P-glycoprotein (P-gp). Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or~~	exposures when administered with ketoconazole and rifampin, respectively. In a drug-drug interaction study (n=8) with ketoconazole, a potent CYP3A4 inhibitor, systemic exposure of trabectedin was increased by approximately 21% (C_{max}) and 66% (AUC_{last}), when trabectedin was given concomitantly with ketoconazole (total daily dose of 400 mg). Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see Dosage and Administration).[i] In a drug-drug interaction study (n=8) with rifampin, a potent CYP3A4 inducer, systemic exposure of trabectedin was decreased by approximately 22% (C_{max}) and 31% (AUC_{last}), when trabectedin was given concomitantly with rifampin (total daily dose of 600 mg). Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampin, phenorbarbital, Saint John's Wort) should be avoided if possible. Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product (see section 4.4). Preclinical data have demonstrated that trabectedin is a substrate to P-glycoprotein (P-gp). Concomitant	

~~elimination. The clinical relevance of this interaction e.g. for CNS toxicity, has not been established and caution should be exercised when concomitantly administering trabectedin with inhibitors of P-gp.~~ ~~Impact of trabectedin on co-administered drugs~~ ~~*In vitro*, trabectedin does not induce or inhibit major cytochrome P450 enzymes.~~ Effects of other substances on trabectedin Interaction studies have only been performed in adults. Since trabectedin is metabolised mainly by CYP3A4,the concentrations of trabectedin in plasma are likely to be increased in patients who are co-administered drugs that potently inhibit the activity of this isoenzyme. Similarly, the co-administration of trabectedin with potent inducers of CPY3A4 may increase the metabolic clearance of trabectedin. Two in vivo drug-drug interaction phase 1 studies have confirmed trends toward increased and decreased trabectedin exposures when administered with ketoconazole and rifampicin, respectively. When ketoconazole was co-administered with trabectedin, the plasma exposure of trabectedin was increased by approximately 21% for C_{max} and 66% for AUC, but no new safety concerns were identified. Close monitoring of	administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The clinical relevance of this interaction e.g. for CNS toxicity, has not been established and caution should be exercised when concomitantly administering trabectedin with inhibitors of P-gp. Impact of trabectedin on co-administered drugs *In vitro*, trabectedin does not induce or inhibit major cytochrome P450 enzymes.	

toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant) and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities (see sections 4.2 and 4.4). When rifampicin was co-administered with trabectedin, it resulted in reduced plasma exposure of trabectedin by approximately 22% for C_{max} and 31% for AUC. Therefore, the concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampicin, phenobarbital, Saint John's Wort) should be avoided if possible (see section 4.4). Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product (see section 4.4). Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such		

situations.		
Yondelis must be reconstituted and further diluted prior to intravenous infusion . A syringe is used to inject 20 ml of sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colorless or slightly yellowish solution~~, to brownish yellow solution~~, essentially free of visible particles.	A syringe is used to inject 20 ml of sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colorless, to brownish yellow solution, essentially free of visible particles	**6.6 Instructions for Use and handling and Disposal**

4.8 Undesirable effects

~~Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of trabectedin based on the comprehensive assessment of the available adverse event information. A causal relationship with trabectedin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.~~

~~The following safety profile of YONDELIS is based on the evaluation in phase II clinical trials of 604 patients assigned to the recommended treatment regime in several cancer types including soft tissue sarcoma, breast cancer, osteosarcoma, ovarian cancer, GIST, melanoma and renal carcinoma.~~

Most patients treated with YONDELIS can be expected to have adverse reactions of any grade (91%) with 10% reporting adverse reactions of grade 3 or 4 severity. The most common adverse reactions of any severity grade were nausea, fatigue, vomiting, anorexia, neutropenia, increases in AST/ALT, anemia and thrombocytopenia. Fatal adverse reactions have occurred in 2.2% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some with sepsis, hepatic dysfunction, renal or multiorgan failure and rhabdomyolysis.

Adverse reactions

The table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Undesirable effects are presented in order of decreasing frequency.

Table 1- Treatment emergent drug related adverse events reported in ≥ 1% of patients in clinical trials assigned to the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]

	YONDELIS n= 604
System Organ Class/Preferred term	**All grades %**
Investigations	
Blood creatinine increased*	31
Blood creatine phosphokinase increased*	27
Blood albumin decreased*	54
Weight decreased	6
Blood and Lymphatic System Disorders	
Anaemia*	95
Leukopenia*	92
Neutropenia*	80
Thrombocytopenia*	40
Febrile neutropenia	2
Nervous System Disorders	
Headache	11
Dysgeusia	4
Peripheral sensory neuropathy	2
Dizziness	2
Paraesthesia	2

Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	5
Gastrointestinal disorders	
Nausea	64
Vomiting	38
Constipation	16
Diarrhea	10
Stomatitis	6
Abdominal pain	5
Dyspepsia	3
Upper abdominal pain	2
Skin and Subcutaneous Tissue Disorders	
Alopecia	3
Musculoskeletal and Connective Tissue Disorders	
Myalgia	5
Arthralgia	2
Back pain	1
Metabolism and Nutrition Disorders	
Dehydration	2
Decreased appetite	21

Infections and Infestations	
Infection	3
Vascular Disorders	
Flushing	2
Hypotension	2
General Disorders and Administration Site Conditions	
Fatigue	56
Asthenia	
Pyrexia	10
Edema	
Edema peripheral	6
Injection site reaction	2
	2
	2
Hepatobiliary Disorders*	
Alanine aminotransferase increased	95
Aspartate aminotransferase increased	
Gamma-glutamyltransferase increased	94
Blood alkaline phosphatase increased	
Hyperbilirubinemia	85
	58
	24
Psychiatric Disorders	
Insomnia	2

*Based on laboratory measurements

Note: Percentages calculated with the number of subjects in each group as denominator.

Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Adverse events are coded using MedDRA version 15.1

Most frequent adverse reactions
Blood and Lymphatic system disorders

Neutropenia: Neutropenia occurred in 80% of patients. Grade 3 and 4 neutropenia occurred in 26% and 24% of patients respectively. Neutropenia followed a predictable pattern of rapid onset and reversibility, and was rarely associated with fever or infection.

Thrombocytopenia: Grade 3 and 4 thrombocytopenia occurred in 11% and 3% of patients respectively. Bleeding events associated to thrombocytopenia occurred in < 1% of patients.

Anaemia: Anaemia occurred in 95% of patients although 53% of patients were anemic before treatment onset. Grade 3 and 4 anemia occurred in 9% and 3% of patients respectively.
Hepatobiliary disorders

AST/ALT increases
Transient grade 3 and grade 4 increases of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed in 37% and 44% (grade 3) and 3% and 7% (grade 4) of the patients, respectively. The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14-15 and less than 2% of cycles had recovery times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

Hyperbilirubinemia: Grades 1 to 2 bilirubin increases were observed in 23% of the patients. Grade 3 hyperbilirubinemia occurred in 1% of patients. Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Severe liver injury:
Manifestations of severe liver injury were uncommon with an incidence of less than 1%. Individual signs and symptoms included jaundice, hepatomegaly and liver pain. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

Other adverse reactions
Nausea, vomiting, diarrhoea and constipation: Nausea and vomiting were reported in 64% and 38% of patients respectively. Grade 3-4 nausea and vomiting were reported in 8% and 9% of patients, respectively. Grade 3-4 diarrhoea and constipation were reported in less than 1% of patients.

Stomatitis: Grade 3-4 mucositis was reported in 2% of the patients.

Fatigue/Asthenia: Grade 3-4 fatigue/asthenia occurred in 11% and 1% of patients respectively.

Anorexia: Grade 3-4 anorexia occurred in 2% of the patients.

CPK elevations and rhabdomyolysis: CPK elevations of any grade were observed in 27% of patients. Grade 3 or 4 increases of CPK were observed in 4% of patients. CPK increases in association with rhabdomyolysis were reported in less than 1% of patients.

Dyspnoea: Grade 3-4 dyspnoea reported as trabectedin related occurred in 2% of the patients.

Alopecia: Alopecia was reported in approximately 3% of patients, of which the majority was grade 1 alopecia.

Hepatic failure
Rare cases of hepatic failure (including cases with fatal outcomes) have been reported in patients with serious underlying medical conditions treated with trabectedin. 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.

Allergic reactions
During clinical trials, hypersensitivity was reported in 2% of patients receiving trabectedin, and most of these cases were Grade 1 or 2 in severity.
During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration (see *Contraindications* and *Warning and Precautions*).

Extravasation and Tissue necrosis
During post marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported (see *Warnings and Precautions*).

Septic shock

Cases of septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience, in patients.

Most patients treated with Yondelis can be expected to have adverse reactions of any grade (91%) and less than one third serious adverse reactions of grade 3 or 4 severity (10%). The most common adverse reactions of any severity grade were neutropenia, nausea, vomiting, increases in AST/ALT, anemia, fatigue, thrombocytopenia, anorexia and diarrhoea.

Fatal adverse reactions have occurred in 1.9% of patients .They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal or multiorgan failure and rhabdomyolysis.

Tabulated summary of adverse reactions

The frequencies of the adverse reactions reported below are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

The table below displays the adverse reactions reported in ≥ 1% of patients treated with the soft tissue sarcoma recommended regimen (1.5 mg/m_2, 24 hour infusion every 3 weeks) according to the standard MedDRA (Medical Dictionary for Regulatory Activities) system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions reported in ≥ 1% of patients with soft tissue sarcoma in clinical trials.**
Infections and Infestations	**Common** Infection
Blood and Lymphatic System Disorders	**Very Common** Neutropenia* (Grade 3 = 26%, Grade 4 = 24%), Thrombocytopenia* (Grade 3 = 11%, Grade 4 = 2%), Anaemia* (Grade 3 = 10%, Grade 4 = 3%), Leukopenia* **Common**

	Febrile neutropenia
Metabolism and Nutrition Disorders	**Very Common** Anorexia (Grade 3-4 < 1%) **Common** Dehydration, Decreased appetite, Hypokalaemia
Psychiatric Disorders	**Common** Insomnia
Nervous System Disorders	**Very Common** Headache **Common** Peripheral sensory neuropathy, Dysgeusia, Dizziness, Paraesthesia
Vascular Disorders	**Common** Hypotension, Flushing
Respiratory, Thoracic and Mediastinal Disorders	**Common** Dyspnoea (Grade 3-4 = 2%), Cough
Gastrointestinal disorders	**Very Common** Vomiting (Grade 3-4 = 6.5%), Nausea (Grade 3-4 = 6%), Constipation (Grade 3-4 < 1%) **Common** Diarrhoea (Grade 3-4 < 1%), Stomatitis (Grade 3-4 < 1%), Abdominal pain, Dyspepsia, Upper abdominal pain

Hepatobiliary Disorders	**Very Common** Hyperbilirubinemia* (Grade 3 = 1%), Alanine aminotransferase increased* (Grade 3 = 38%, Grade 4 = 3%), Aspartate aminotransferase increased* (Grade 3 = 44%, Grade 4 = 7%), Blood alkaline phosphatase increased*, Gamma-glutamyltransferase increased*
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia
Musculoskeletal and Connective Tissue Disorders	**Common** Myalgia, Arthralgia, Back pain
General Disorders and Administration Site Conditions	**Very Common** Fatigue (Grade 3-4 = 9%), Asthenia (Grade 3-4 = 1%) **Common** Pyrexia, Oedema, Oedema peripheral, Injection site reaction
Investigations	**Very Common** Blood creatine phosphokinase increased* (Grade 3-4 = 4%), Blood creatinine increased*, Blood albumin decreased* **Common** Weight decreased

* Derived from laboratory data

Description of selected adverse reactions

Most frequent adverse reactions

Blood and lymphatic system disorders

Neutropenia:

Neutropenia is the most common haematological toxicity. It followed a predictable pattern of rapid onset and reversibility, and was rarely associated with fever or infection. Neutrophil nadirs occurred at a median of 15 days and recovered within a week. The analysis per cycle performed in patients treated with the monotherapy regimen showed neutropenia of grade 3 and 4 in approximately 19% and 8% of cycles respectively. In this population febrile neutropenia occurred in 2% of patients and in < 1% of cycles.

Thrombocytopenia:

Bleeding events associated to thrombocytopenia occurred in < 1% of patients treated with the monotherapy regimen. The analysis per cycle performed in these patients showed thrombocytopenia of grade 3 and 4 in approximately 3% and < 1% of cycles respectively.

Anaemia:

Anaemia occurred in 93% of patients treated with the monotherapy .The percentages of patients anaemic at baseline were 46%. The analysis per cycle performed in patients treated with the monotherapy regimen showed anaemia of grade 3 and 4 in approximately 3% and 1% of cycles respectively.

Hepatobiliary disorders

AST/ALT increases:

The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14-15 (see section 4.4). The analysis per cycle performed in patients treated with the monotherapy regimen showed grade 3 elevations of AST and ALT in 12% and 20% of cycles respectively. Grade 4 elevations of AST and ALT occurred in 1% and 2% of cycles respectively. Most transaminase

elevations improved to grade 1 or to pre-retreatment levels within 15 days, and less than 2% of cycles had recovering times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

Hyperbilirubinemia:
Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Liver function tests predicting severe toxicity (meeting Hy´s law) and clinical manifestations of severe hepatic injury were uncommon with a lower than 1% incidence of individual signs and symptoms including jaundice, hepatomegaly or liver pain. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

Other adverse reactions

CPK elevations and rhabdomyolysis: CPK elevations of any grade were observed in 23-26% of patients. CPK increases in association with rhabdomyolysis were reported in less than 1% of patients.

Alopecia: Alopecia was reported in approximately 3% of patients, of which the majority was grade 1 alopecia.

Hepatic failure: 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.

Allergic Reactions: During clinical trials, hypersensitivity was reported in 2% of patients receiving trabectedin, 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 (see sections 4.3 and 4.4).

Extravasation and Tissue necrosis: During post-marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported (see section 4.4).

Septic shock: Cases of septic shock, some of which were fatal, have been uncommonly reported in clinical studies and postmarketing experience.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך.....17.1.16