הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך: 31/07/2016

שם תכשיר באנגלית ומספר רישום: Halaven 148-18-33511

שם בעל הרישום: Neopharm Scientific Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
4. CLINICAL PARTICULARS **4.1 Therapeutic indications** **4.2 Posology and method of administration**		HALAVEN is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1). The safety and efficacy of HALAVEN in children from birth to 18 years of age have not yet been established in soft tissue sarcoma. No data are available.

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Unless otherwise noted, the table shows the incidence rates of adverse reactions observed in breast cancer and soft tissue sarcoma patients who received the recommended dose in ~~five~~ Phase 2 and Phase 3 studies. Please see Table 1 below *Neutropenia* The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 10^9/l) was 8 days. Neutrophil counts of < 0.5 x 10^9/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study. Neutropenia was reported as a Treatment Emergent Adverse Event (TEAE) in 151/404 (37.4% for all grades) in the sarcoma population, compared with 902/1559 (57.9% for all grades) in the breast cancer population. The combined grouped TEAE and neutrophil laboratory abnormality frequencies were 307/404 (76.0%) and 1314/1559 (84.3%), respectively. The median duration of treatment was 12.0 weeks for sarcoma patients and 15.9 weeks for breast cancer patients. Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Out of 1963 breast	Unless otherwise noted, the table shows the incidence rates of adverse reactions observed in 1503 breast cancer patients who received the recommended dose in five Phase 2 and two Phase 3 studies. Please see Table 2 *Neutropenia* The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 10^9/l) was 8 days. Neutrophil counts of < 0.5 x 10^9/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study.	**4.4 Special warnings and precautions for use** **4.8 Undesirable effects**

cancer and soft tissue sarcoma patients who received eribulin at the recommended dose in clinical trials there was one fatal event each of neutropenic sepsis (0.1%) and febrile neutropenia (0.1%). In addition there were 3 fatal events of sepsis (0.2%) and one of septic shock (0.1%). *Peripheral neuropathy* … Out of the 404 sarcoma patients, 2 patients discontinued treatment with eribulin due to peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 18.4 weeks. Development of Grade 3 or 4 peripheral neuropathy occurred in 7.4% of breast cancer patients and 3.5% of sarcoma patients.	*Peripheral neuropathy* Development of Grade 3 or 4 peripheral neuropathy occurred in 7.7% of eribulin treated breast cancer patients.	

Table 1

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	Common (Frequency %)	Uncommon (Frequency %)	Rare

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Infections and infestations		Urinary tract infection (8. 5%) (G3/4: 0. 7%) Pneumonia (1. 6%) (G3/4: 1.0%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis Herpes zoster	Sepsis (0.5%) (G3/4: 0. 5%)a Neutropenic sepsis (0. 2%) (G3/4: 0.2%)a Septic Shock (0.2%) (G3/4:0.2%)a	
Blood and lymphatic system disorders	Neutropenia (053.6%) (G3/4: 46.0%) Leukopenia (27.9%) (G3/4: 17.0%) Anaemia (21.8%) (G3/4: 3.0%)	Lymphopenia (5.7%) (G3/4: 2.1%) Febrile neutropenia (4.5%) (G3/4: 4. 4%)a Thrombocytopenia (4.2%) (G3/4: 0.7%)		Disseminated intravascular coagulation[b]
Metabolism and nutrition disorders	Decreased appetite (22.5%) (G3/4: 0.7%)d	Hypokalaemia (6. 8%) (G3/4: 2.0%) Hypomagnesaemia (2. 8%) (G3/4: 0. 3%) Dehydration (2.8 %) (G3/4: 0.5%) d Hyperglycaemia Hypophosphataemia		

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathyc (35.9%) (G3/4:.3%) Headache (17.5%) (G3/4: 0.7%)	Dysgeusia Dizziness (9.0%) (G3/4: 0. 4%) d Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (5.8%) (G3/4: 0.1%) d Conjunctivitis		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders		Tachycardia		
Vascular disorders		Hot flush Pulmonary embolism (1.3%) (G3/4: 1.1%)a	Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (15.2%)a (G3/4: 3.5%) a Cough (15.0%) (G3/4: 0.5%) d	Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease (0.2%) (G3/4: 0.1%)	

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Gastrointestinal disorders	Nausea (35.7%) d (G3/4: 1.1%) Constipation (22.3%) (G3/4: 0. 7%) d Diarrhoea (18.7%) (G3/4: 0.8%) Vomiting (18.1%) (G3/4: 1.0%)	Abdominal pain Stomatitis (11.1%) (G3/4: 1.0%) d Dry mouth Dyspepsia (6.5%) (G3/4: 0. 3%) d Gastrooesophageal reflux disease Abdominal distension	Mouth ulceration Pancreatitis	
Hepatobiliary disorders		Aspartate aminotransferase increased (7.7%) (G3/4: 1.4%) d Alanine aminotransferase increased (7.6%) (G3/4: 1.9%)d Gamma glutamyl transferase increased (1.7%) (G3/4: 0.9%) d Hyperbilirubinaemia (1.4%) (G3/4: 0.4%)	Hepatotoxicity (0.8%) (G3/4: 0.6%)	

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Skin and subcutaneous tissue disorders	Alopecia	Rash (4.9%) (G3/4: 0.1%) Pruritus (3.9%) (G3/4: 0.1%) Nail disorder Night sweats Dry skin Erythema Hyperhidrosis Palmar plantar erythrodysaesthesia (1.0%) (G3/4: 0.1%)d	Angioedema	
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (20.4%) (G3/4: 1. 0%) Back pain (12.8%) (G3/4:1.5%) Pain in extremity (10.0%) (G3/4: 0.7%) d	Bone pain (6.7%) (G3/4: 1. 2%) Muscle spasms (5. 3%) (G3/4: 0.1%) d Musculoskeletal pain Musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
General disorders and administration site conditions	Fatigue/Asthenia (53.2%) (G3/4 : 7. 7%) Pyrexia (21.8%) (G3/4: 0. 7%)	Mucosal Inflammation (6.4%) (G3/4: 0.9%)[d] Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11. 4%) (G3/4: 0. 4%)[d]			

Table 2

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Infections and infestations		Urinary tract infection (8.08%) (G3/4: 0.5%) Pneumonia (1.2%) (G3/4: 0.8%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis	Sepsis (0.5%) (G3/4: 0.2%)a Neutropenic sepsis (0.1%) (G3/4: 0. 1%) Herpes zoster	
Blood and lymphatic system disorders	Neutropenia (57. %) (G3/4: 49.7%) Leukopenia (29.3%) (G3/4: 17.3%) Anaemia (20.6%) (G3/4: 2.0%)	Lymphopenia (4.9%) (G3/4: 1.4%) Febrile neutropenia (4.7%) (G3/4: 4.5%)a Thrombocytopenia (4.3%) (G3/4: 0.7%)		Disseminated intravascular coagulation[b]

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Metabolism and nutrition disorders	Decreased appetite (21.9%) (G3/4: 0.7%)	Hypokalaemia (6.1%) (G3/4: 1. %) Hypomagnesaemia (2.9%) (G3/4: 0.2%) Dehydration (2.8 %) (G3/4: 0.5%) Hyperglycaemia Hypophosphataemi a		
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathyc (35.6%) (G3/4: 7.6%) Headache (17.2%) (G3/4: 0.8%)	Dysgeusia Dizziness (7.9%) (G3/4: 0.5%) Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (6.0%) (G3/4: 0.1%) Conjunctivitis		
Ear and labyrinth disorders		Vertigo	Tinnitus	
Cardiac disorders		Tachycardia		

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Vascular disorders		Hot flush	Deep vein thrombosis Pulmonary embolism	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (13. %)a (G3/4: 3.1%) Cough (13.6 %) (G3/4: 0.6%)	Oropharyngeal pain Epistaxis Rhinorrhoea		Interstitial lung disease
Gastrointestinal disorders	Nausea (33.8%) (G3/4: 1.1%) Constipation (19.6%) (G3/4: 0.6%) Diarrhoea (17.9%) (G3/4: 0.8%) Vomiting (17.6%) (G3/4: 0.9%)	Abdominal pain Stomatitis (9.3%) (G3/4: 0.8%) Dry mouth Dyspepsia (5.9%) (G3/4: 0.2%) Gastrooesophageal reflux disease Mouth ulceration Abdominal distension		Pancreatitis[b]

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Hepatobiliary disorders		Alanine aminotransferase increased (7.6%) (G3/4: 2.1%)d Aspartate aminotransferase increased (7.4%) (G3/4: 1.5%) Gamma glutamyl transferase increased (1.8%) (G3/4: 0.9%) Hyperbilirubinaemia (1.5%) (G3/4: 0.3%)	Hepatotoxicity (1.0%) (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus (3.9%) (G3/4: 0.1%) Nail disorder Night sweats Dry skin Erythema Hyperhidrosis	Palmar plantar erythrodysaesthesia	Angioedema

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare**
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (19.4%) (G3/4: 1.1%) Back pain (13.0%) (G3/4:1.5%) Pain in extremity (10.0%) (G3/4: 0.7%)	Bone pain (9.6%) (G3/4: 1.7%) Muscle spasms (5.1%) (G3/4: 0.1%) Musculoskeletal pain and musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	
General disorders and administration site conditions	Fatigue/Asthenia (47.9%) (G3/4 : 7.8%) Pyrexia (20.4%) (G3/4: 0.6%)	Mucosal Inflammation (8.3%) (G3/4: 1.1%)d Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11.34%) (G3/4: 0. 3%)			