הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך _____ 02.04.2014_____

שם תכשיר באנגלית Evoltra

מספר רישום 140 11 31946

שם בעל הרישום __סאנופי-אוונטיס ישראל _____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
		Indication
		Contraindications
מידע שהתווסף ומהווה החמרה מסומן בצהוב , מידע שהוסר מסומן באדום עם קו מחיקה (יש להדגיש כי מוזכר כאן רק החלק בו הייתה החמרה, מידע מלא של סעיף זה ניתן למצוא בעלון המלא): ~~There is no experience in patients with renal insufficiency (serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys. Therefore~~, The limited data available indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see sections 4.4 and 5.2). Clofarabine is contraindicated in patients with severe renal insufficiency (see section 4.3) and should be used with caution in patients with mild to moderate renal insufficiency (see section 4.4). Patients with moderate renal impairment (creatinine clearance 30 – <60 ml/min) require a 50% dose reduction (see section 5.2). ~~To date, there are insufficient data on the pharmacokinetics of clofarabine in patients with decreased creatinine clearance to advise a dose reduction in such patients. However, these limited data indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see sections 4.4 and 5.2).~~		**Posology, Dosage & Administration**
מידע שהתווסף ומהווה החמרה מסומן בצהוב , מידע שהוסר מסומן באדום עם קו מחיקה (יש להדגיש כי מוזכר כאן רק החלק בו הייתה החמרה, מידע מלא של סעיף זה ניתן למצוא בעלון המלא): Hemorrhage, including cerebral, gastrointestinal and pulmonary hemorrhage, has been reported and may be fatal. The majority of the cases were associated with thrombocytopenia (*see 4.8 Undersible effects*) …… Occurrences of enterocolitis, including neutropaenic colitis and *C. difficile* colitis,		**Special Warnings and Special Precautions for Use**

caecitis, have been reported during treatment with clofarabine. This has occurred more frequently within 30 days of treatment, and in the setting of combination chemotherapy. Enterocolitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcome (see section 4.8). Patients should be monitored for signs and symptoms of enterocolitis. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported (see section 4.8). Clofarabine must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected. …….. There is no clinical study experience in paediatric patients with renal insufficiency (defined in clinical studies as serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys. ~~Therefore, clofarabine should be used with caution in patients with mild to moderate renal insufficiency (see sections 4.2 and 4.3). To date, there are insufficient data on the pharmacokinetics of clofarabine in patients with decreased creatinine clearance to advise a dose reduction in such patients. However, these limited~~ Pharmacokinetic data indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see sections ~~4.2 and~~ 5.2). Therefore, clofarabine should be used with caution in patients with mild to moderate renal insufficiency (see sections 4.2 for dose adjustment)~~.~~ The safety profile of clofarabine has not been established in patients with severe renal impairment or patients receiving renal replacement therapy (see section 4.3). …… ……. Patients who have previously received a hematopoietic stem cell transplant (HSCT) may be at higher risk for hepatotoxicity suggestive of veno-occlusive disease (VOD) following treatment with clofarabine (40 mg/m^2) when used in combination with etoposide (100 mg/m^2) and cyclophosphamide (440 mg/m^2). Occurrences of enterocolitis, including neutropenic colitis, cecitis, and C. difficile colitis, have been reported during treatment with clofarabine. This has occurred more frequently within 30 days of treatment, and in the setting of combination chemotherapy. Enterocolitis may lead to necrosis, perforation, hemorrhage or sepsis complications and may be associated with fatal outcome (see4.8 Undesirable effects). Patients should be monitored for signs and symptoms of enterocolitis.		

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported (see 4.8 Undesirable effects). Clofarabine must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected. In the post-marketing period, following treatment with clofarabine, serious hepatotoxic adverse reactions of VOD in paediatric and adult patients have been associated with a fatal outcome. Most patients received conditioning regimens that included busulfan, melphalan, and/or the combination of cyclophosphamide and total body irradiation. Severe hepatotoxic events have been reported in a~~n ongoing~~ Phase 1/2 combination study of clofarabine in paediatric patients with relapsed or refractory acute leukemia.		
		Fertility, pregnancy and lactation
מידע שהתווסף ומהווה החמרה מסומן בצהוב , מידע שהוסר מסומן באדום עם קו מחיקה (יש להדגיש כי מוזכר כאן רק החלק בו הייתה החמרה, מידע מלא של סעיף זה ניתן למצוא בעלון המלא): Gastrointestinal disorders: *Very common:* Vomiting, nausea, diarrhoea *Common:* Mouth haemorrhage, gingival bleeding, haematemesis, abdominal pain, stomatitis, upper abdominal pain, proctalgia, mouth ulceration *Frequency not known:* Pancreatitis, elevations in serum amylase and lipase, enterocolitis, neutropaenic colitis, caecitis **……..** Blood and lymphatic system disorders: the most frequent haematological laboratory abnormalities observed in patients treated with clofarabine were anaemia (83.3%; 95/114); leucopaenia (87.7%; 100/114); lymphopaenia (82.3%; 93/113), neutropaenia (63.7%; 72/113), and thrombocytopaenia (80.7%; 92/114).The majority of these events were of grade □3. During the post-marketing period prolonged cytopaenias (thrombocytopaenia, anaemia, neutropaenia and leukopaenia) and bone marrow failure have been reported. Bleeding events have been observed in the setting of thrombocytopaenia. …… Infections and infestations: Forty-eight percent of patients had one or more ongoing infections prior to receiving treatment with clofarabine. A total of 83% of patients experienced at least 1 infection after clofarabine treatment, including fungal, viral and bacterial infections (see section 4.4). Twenty-one (18.3%) events were considered to be related to clofarabine of which catheter related infection (1 event), sepsis (2 events) and septic shock (2 events; 1 patient died (see		**Undesirable effects**

above)) were considered to be serious. During the post-marketing period, bacterial, fungal and viral infections have been reported and may be fatal. These infections may lead to septic shock, respiratory failure, renal failure, and/or multi-organ failure. Hemorrhage, including cerebral and pulmonary hemorrhage, has been reported and may be fatal …… Hepato-biliary disorders: The liver is a potential target organ for clofarabine toxicity and 25.2% of patients experienced at least one hepato-biliary disorders adverse event (see sections 4.3 and 4.4). Six events were considered to be related to clofarabine of which acute cholecystitis (1 event), cholelithiasis (1 event), hepatocellular damage (1 event; patient died (see above)) and hyperbilirubinaemia (1 event; the patient discontinued therapy (see above)) were considered to be serious. Two paediatric reports (1.7%) of veno-occlusive disease (VOD) were considered related to study drug. VOD cases reported during the post-marketing period in paediatric and adult patients have been associated with a fatal outcome (see section 4.4). …… Capillary leak syndrome cases reported during the post-marketing period have been associated with a fatal outcome (See section 4.4). Gastrointestinal disorders: Occurrences of enterocolitis, including neutropaenic colitis, caecitis, and *C. difficile* colitis have been reported during treatment with clofarabine. Enterocolitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcome (see section 4.4). Gastrointestinal haemorrhage has been observed and may be associated with a fatal outcome. Metabolism and nutrition disorders: hyponatremia Skin and subcutaneous disorders: Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported in patients who were receiving or had recently been treated with clofarabine. Other exfoliative conditions have also been reported.		
מידע שהתווסף ומהווה החמרה מסומן בצהוב , מידע שהוסר מסומן באדום עם קו מחיקה (יש להדגיש כי מוזכר כאן רק החלק בו הייתה החמרה, מידע מלא של סעיף זה ניתן למצוא בעלון המלא): *Patients with renal insufficiency*~~: There is no experience in patients with renal insufficiency (serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys (see sections 4.3 and 4.4).~~ To date, there		**Pharmacokinetic properties**

are limited data on the pharmacokinetics of clofarabine in paediatric patients with decreased creatinine clearance. However, these data indicate that clofarabine may accumulate in such patients (see figure below ~~and sections 4.2 and 4.4~~). Population pharmacokinetic data from adult and paediatric patients suggest that patients with stable moderate renal impairment (creatinine clearance 30 – <60 ml/min) receiving a 50% dose reduction achieve similar clofarabine exposure to those with normal renal function receiving a standard dose.		