

**הודעה על החמרה (מידע בטיחות) בעלון לרופא**

תאריך: 17.03.14

שם תכשיר באנגלית: Mepact

מספר רישום: 147-07-33425-00

שם בעל הרישום: מדיסון פארמה בע"מ

השינויים בעלון מסומנים על רקע צהוב

**בעלון לרופא**

פרטים על השינויים המבוקשים/ים		
טקסט חדש	טקסט נוכחי	פרק בעלון
MEPACT 4 mg powder for suspension for infusion for concentrate for dispersion for infusion.	MEPACT 4 mg powder for suspension for infusion	<b>1.NAME OF THE MEDICINL PRODUCT</b>
<p><i>Paediatric patients</i> The safety and efficacy of MEPACT have been established in children from the age of 2 years. It is not recommended for use in children below the age of 2 due to a lack of data on efficacy and safety in this age group</p> <p><i>Paediatric population &lt;2 years</i></p> <p>The safety and efficacy of mifamurtide in children aged 0 to 2 years have not been established. No data are available.</p> <p><i>Elderly patients Adults &gt;30 years</i></p>	<p><i>Paediatric patients</i> The safety and efficacy of MEPACT have been established in children from the age of 2 years. It is not recommended for use in children below the age of 2 due to a lack of data on efficacy and safety in this age group</p> <p><i>Elderly patients</i></p>	<b>4.2 Posology and Method of Administration</b>
<p><b>4.7 Fertility, Ppregnancy and lactation</b></p> <p><u>Pregnancy</u> There are no data from the use of mifamurtide in pregnant patients women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). MEPACT mifanurtide</p>	<p><b>4.6 Pregnancy and lactation</b></p> <p><u>Pregnancy</u> There are no data from the use of mifamurtide in pregnant patients. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). MEPACT should not be used during pregnancy and in women not using</p>	<b>Fertility, Pregnancy and Lactation</b>

<p><del>should not be used</del> not recommended for use during pregnancy and in women of childbearing potential not using effective contraception.</p> <p><b>Lactation Breast-feeding</b></p> <p>It is unknown whether mifamurtide is excreted in human milk. The excretion of mifamurtide in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of MEPACT mifamurtide therapy to the woman.</p> <p><b>Fertility</b></p> <p>No dedicated fertility studies have been conducted with mifamurtide (see section 5.3).</p>	<p>effective contraception.</p> <p><u>Lactation</u></p> <p>It is unknown whether mifamurtide is excreted in human milk. The excretion of mifamurtide in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of MEPACT therapy to the woman.</p>	
--	---	--

Undesirable effects	Undesirable effects	Undesirable effects
<p><b>Summary of the safety profile</b>  Mifamurtide was studied as a single agent in Each of the 248 patients treated with mostly advanced malignancies MEPACT during the early single arm phase single arm I and II clinical studies in patients with mostly advanced malignancies experienced at least one undesirable effect.</p> <p>The most frequent adverse reactions, occurring in &gt;50% of patients, were chills, pyrexia, fatigue, nausea, tachyarrhythmia and headache. Many of the most frequently very commonly reported undesirable effects adverse reactions as shown in the following summary table are thought to be related to the mechanism of action of mifamurtide (see Table 1). The majority of these events were reported as either mild or moderate. This profile is consistent whether summarising all early studies (n=248) or only those studies in osteosarcoma (n=51). It is likely that these undesirable effects adverse reactions also occurred in the large randomised study, but they were not recorded because only serious and life-threatening adverse reactions were collected in that study.</p> <p><i>Blood and lymphatic system disorders</i>  Anaemia has most very commonly been reported when MEPACT mifamurtide is used in conjunction with chemotherapeutic agents. In a randomised controlled trial study, the incidence of myeloid malignancy (acute myeloid leukaemia/myelodysplastic syndrome) was the same in patients receiving MEPACT plus chemotherapy as in patients receiving only chemotherapy (approximately 2.15%).</p> <p><i>Metabolism and nutritional disorders</i>  Anorexia (21%) was very commonly reported in trials of MEPACT in late stage cancer patients- phase I and II studies of mifamurtide.</p>	<p>Each of the 248 patients treated with MEPACT during the early phase single arm studies in patients with mostly advanced malignancies experienced at least one undesirable effect. Many of the most frequently reported undesirable effects as shown in the following summary table are thought to be related to the mechanism of action of mifamurtide. The majority of these events were reported as either mild or moderate. This profile is consistent whether summarising all early studies (n=248) or only those studies in osteosarcoma (n=51). It is likely that undesirable effects also occurred in the large randomised study, but they were not recorded because only serious and life-threatening adverse reactions were collected in that study.</p> <p><i>Blood and lymphatic system disorders</i>  Anaemia has most commonly been reported when MEPACT is used in conjunction with chemotherapeutic agents. In a randomised controlled trial, the incidence of myeloid malignancy (acute myeloid leukaemia/myelodysplastic syndrome) was the same in patients receiving MEPACT plus chemotherapy as in patients receiving only chemotherapy (approximately 2.5%).</p> <p><u>Metabolism and nutritional disorders</u>  Anorexia (21%) was very commonly reported in trials of MEPACT in late stage cancer patients.</p>	

<p><i>Nervous system disorders</i>  Consistent with other generalised symptoms, the most common nervous system disorders were headache (50%) and dizziness (17%).  One patient in the phase III study experienced 2 episodes of Grade 4 seizure while on study therapy with chemotherapy and mifamurtide. The second episode involved multiple grand mal seizures over the course of days. Mifamurtide treatment was continued for the remainder of the study without seizure recurrence.</p> <p><i>Cardiac and vascular disorders</i>  Mild-moderate tachycardia (50%), hypertension (26%) and hypotension (29%) were very commonly reported in uncontrolled trials studies of MEPACT mifanurtide. One serious incident of subacute thrombosis was reported in early studies, but no serious cardiac events were associated with MEPACT mifanurtide in a large randomised controlled trial study.</p> <p><i>Musculoskeletal and connective tissue disorders</i>  Low grade pain was very common in patients receiving MEPACT mifanurtide, including myalgia (31%), back pain (15%), extremity pain (12%) and arthralgia (10%).</p> <p><i>Immune system disorders</i>  In a phase I study, there was one report of severe allergic reaction occurring after the first infusion of mifamurtide at 6 mg/m<sup>2</sup> dose level. The patient experienced shaking, chills, fever, nausea, vomiting, uncontrollable coughing, shortness of breath, cyanotic lips, dizziness, weakness, hypotension, tachycardia, hypertension and hypothermia leading to study discontinuation. There was also one report of a grade 4 allergic reaction (hypertension) requiring hospitalization in the phase III study (see section 4.4).</p>	<p><i>Nervous system disorders</i>  Consistent with other generalised symptoms, the most common nervous system disorders were headache (50%) and dizziness (17%).</p> <p><i>Cardiac and vascular disorders</i>  Mild-moderate tachycardia (50%), hypertension (26%) and hypotension (29%) were commonly reported in uncontrolled trials of MEPACT.</p> <p><i>Musculoskeletal and connective tissue disorders</i>  Low grade pain was common in patients receiving MEPACT, including myalgia (31%), back pain (15%), extremity pain (12%) and arthralgia (10%).</p> <p style="text-align: center;">לא קיים</p>	
--	---	--

<p><b>Reporting of suspected adverse reactions</b> 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. Healthcare professionals are asked to report any suspected adverse reactions.</p>	<p><b>לא קיים</b></p>	
<p><b>5.1 Pharmacodynamic properties</b></p> <p>Pharmacotherapeutic group: Immunostimulants, Other immunostimulants, Other cytokines and immunomodulators, ATC code: L03AX15</p>	<p><b>5.1 Pharmacodynamic properties</b></p> <p>Pharmacotherapeutic group: Other cytokines and immunomodulators, ATC code: L03AX15</p>	<p><b>Pharmacodynamic properties</b></p>
<p style="text-align: center;"><b>Nature and contents of container</b></p> <p>50 ml type I glass vial with a grey butyl rubber stopper, aluminium seal and plastic flip-off cap, containing 4 mg of mifamurtide.</p> <p>Each carton contains one vial and one single-use, non-pyrogenic, latex-free sterile filter for MEPACT supplied in a PVC-grade blister.</p>	<p style="text-align: center;"><b>Nature and contents of container</b></p> <p>50 ml type I glass vial with a grey butyl rubber stopper, aluminium seal and plastic flip-off cap, containing 4 mg of mifamurtide.</p> <p>Each carton contains one vial and one single-use, non-pyrogenic, latex-free sterile Filter for MEPACT supplied in a PVC-grade blister.</p>	<p style="text-align: center;"><b>Nature and contents of container</b></p>

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

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