הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך 20.06.13

שם תכשיר באנגלית ומספר הרישום MEPACT 147 07 33425 00

שם בעל הרישום _____Medison Pharma Ltd._____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**

Patients with impaired renal or hepatic function There are no clinically meaningful effects of mild to moderate renal (creatinine clearance (CrCL) ≥ 30ml/min) or hepatic impairment (Child-Pugh class A or B) on the pharmacokinetics of mifamurtide; therefore, dose adjustments are not necessary for these patients. However, as the variability in pharmacokinetics of mifamurtide is greater in subjects with moderate hepatic impairment (see Section 5.2), and safety data in patients with moderate hepatic impairment is limited, caution when administering mifamurtide to patients with moderate hepatic impairment is recommended.	*Patients with impaired renal or hepatic function* The pharmacokinetics of mifamurtide in patients with renal or hepatic impairment have not been formally studied. Caution should be used in these patients because dose adjustment information is not available.	**4.2 Posology and method of administration**
The pharmacokinetics of mifamurtide have been characterized in healthy adult subjects following a 4 mg intravenous infusion and in paediatric and adult patients with osteosarcoma following a 2 mg/m^2 intravenous infusion. In 21 healthy adult subjects mifamurtide was cleared rapidly from serum (minutes) with a half-life of 2.05 ± 0.40 hours, resulting in a very low serum concentration of total (liposomal and free) mifamurtide. The mean AUC was 17.0 ±4.86 h x nM and Cmax was 15.7 ± 3.72 nM. In 28 osteosarcoma patients aged 6 to 39 years serum total (liposomal and free) mifamurtide concentrations declined rapidly with a mean half-life of 2.04 ± 0.456 hours. BSA-normalized clearance and half-life were similar across the age range and consistent with that determined in healthy adult subjects, supporting the recommended dose of 2 mg/m^2. In a separate study in 14 patients, mean serum concentration-time curves of total and free mifamurtide that were assessed after the first infusion of MEPACT and after a last infusion 11 or 12 weeks later, were almost superimposable and the mean AUC values of the free mifamurtide after the first and last infusion were similar. These data	After intravenous administration in 21 healthy adult subjects mifamurtide was cleared rapidly from plasma (minutes), resulting in a very low plasma concentration of total (liposomal and free) mifamurtide. The mean AUC was 17.0 +/- 4.71 h x nM and Cmax was 15.7 +/- 3.72 nM. In separate study in 14 patients, mean serum concentration-time curves of total and free mifamurtide that were assessed after the first infusion of MEPACT and after a last infusion 11 or 12 weeks later, were almost superimposable and the mean AUC values of the free mifamurtide after the first and last infusion were similar. These data indicate that neither total nor free mifamurtide accumulated during the treatment period. At 6 hours after injection of radiolabelled liposomes containing 6 mg mifamurtide, radioactivity was found in liver, spleen, nasopharynx, thyroid, and, to a lesser extent, in lung. The liposomes were phagocytosed by cells of the reticuloendothelial system. In 2 of 4 patients with lung metastases, radioactivity was associated with lung metastases. Mean half-life of radiolabelled material was biphasic with an α phase of about 15 minutes and a	**5.2 Pharmacokinetic properties**

indicate that neither total nor free mifamurtide accumulated during the treatment period. At 6 hours after injection of radiolabelled liposomes containing 1 mg mifamurtide, radioactivity was found in liver, spleen, nasopharynx, thyroid, and, to a lesser extent, in lung. The liposomes were phagocytosed by cells of the reticuloendothelial system. In 2 of 4 patients with lung metastases, radioactivity was associated with lung metastases. Metabolism of L-MTP-PE has not been studied in humans. After injection of radiolabelled liposomes containing mifamurtide, mean half-life of radiolabelled material was biphasic with an α phase of about 15 minutes and a terminal half-life of approximately 18 hours.	terminal half-life of approximately 18 hours.	

Renal Impairment The pharmacokinetics of a single 4mg dose of mifamurtide following a 1 hour intravenous infusion were evaluated in adult volunteers with mild (n=9) or moderate (n=8) renal impairment and in age- ,sex-, and weight-matched healthy adults with normal renal function (n=16). There was no effect of mild (50 mL/min ≤ CLcr ≤80 mL/min) or moderate (30 mL/min ≤ CLcr < 50 mL/min) renal insufficiency on the clearance of t0otal MTP-PE, when compared with that observed in healthy adult subjects with normal renal function (CLcr > 80 mL/min). Additionally, the systemic exposures (AUCinf) of free (non-liposome associated) MTP-PE in mild or moderate renal insufficiency were similar to those observed in healthy adult subjects with normal renal function. Hepatic Impairment The pharmacokinetics of a single 4mg dose of mifamurtide following a 1 hour intravenous infusion were evaluated in adult volunteers with mild (Child-Pugh class A; n=9) or moderate (Child-Pugh class B; n=8) hepatic impairment and in age- ,sex- , and weight-matched healthy adults with normal hepatic function (n=19). There was no effect of mild hepatic impairment on the systemic exposure (AUCinf) of total MTP-PE. Moderate hepatic impairment resulted in a small increase in AUCinf of total MTP-PE, with the geometric least square mean ratio (expressed as %) for moderate hepatic impairment in reference to the matched normal hepatic function group being 119% (90% CI: 94.1%-151%). Pharmacokinetic variability was higher in the moderate hepatic impairment group (co-efficient of variation in systemic exposure [AUCinf] was 50% versus <30% in the other hepatic function groups). Mean half-lives of total and free MTP-PE in mild hepatic impairment were 2.02 hours and 1.99 hours, respectively, and were comparable to those in subjects with normal hepatic function (2.15 hours and 2.26 hours, respectively).	**Section not included**	**Special Populations**

Mean half-lives of total and free MTP-PE in moderate hepatic impairment were 3.21 hours and 3.15 hours, respectively. Additionally, the geometric mean plasma AUCinf of free (non-liposome associated) MTP-PE in mild and moderate hepatic impairment were 47% higher than the corresponding values in the matched normal hepatic function groups. These changes were not considered to be clinically meaningful as the maximum tolerated dose (4-6 mg/m^2) of mifamurtide is 2-3 times the recommended dose (2 mg/m^2).		

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