הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

אושר – 11.16

תאריך _____08/08/16

שם תכשיר באנגלית ומספר הרישום 153-84-34276-00 Defitelio 80 mg/ml_____

שם בעל הרישום ___מדיסון פארמה בע"מ_____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Renal ~~and Hepatic~~ Impairment Dose adjustment is not required for patients with renal impairment or who are on intermittent haemodialysis (see section 5.2). *Hepatic Impairment* No formal pharmacokinetic studies have been performed in patients with ~~renal or~~ hepatic impairment, however, the medicinal product has been used in clinical trials of ~~in~~ patients developing ~~renal and~~ hepatic impairment without dose adjustment with no safety issues identified. No dose adjustment is therefore recommended but careful monitoring of patients should be undertaken (see section 5.2).	*Renal and Hepatic Impairment* No formal pharmacokinetic studies have been performed in patients with renal or hepatic impairment, however, the medicinal product has been used in clinical trials in patients developing renal and hepatic impairment without dose adjustment with no safety issues identified. No dose adjustment is therefore recommended but	**4.2 Posology**

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<td>4.9 Overdose

There is no specific antidote for overdose and treatment should be symptomatic.
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<td>5.2 Pharmacokinetic properties

<u>Absorption and Distribution</u>

In 52 healthy volunteers, after a single 6.25 mg/kg dose of Defitelio given as a 2-hour infusion, the pharmacokinetic parameters were as follows:

Table 4. Defitelio pharmacokinetic parameters after intravenous infusion of 6.25 mg/kg to healthy subjects

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<tr><td>C_{max} (µg/mL)</td><td>17.3 ± 3.83</td></tr>
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peaked at the end of the infusion period and declined thereafter with a rapid clearance and most of samples were undetectable 3.5 hours after the start of the infusion. Pharmacokinetic modelling simulation analysis showed that Defitelio plasma concentrations do not accumulate upon multiple doses administration and with doses up t o 4-fold the therapeutic dose. Volume of distribution is around 10 L ~~and Defitelio is not bound to plasma proteins.~~ *In vitro* studies demonstrate that 93% of Defitelio is bound to plasma proteins. <u>Elimination</u> After administration of the therapeutic dose (6.25 mg/kg) to healthy subjects, an average of 9.48% of the total dose administered is excreted in urine as unchanged defibrotide in 24 hours, with the majority excreted during the first collection interval of 0-4 hours (approximately 98%). ~~98% of Defitelio is excreted unchanged in the urine in the first 4 hours after the start of the infusion. The remaining 2% is excreted within 24 hours.~~ <u>Special Populations</u> <u>*Renal Impairment*</u> Six patients with an estimated glomerular filtration rate <30 mL/min/1.73m^2 (calculated using the Modification of Diet in Renal Disease equation) and not currently on dialysis were compared to 6 healthy subjects with similar baseline demographics. Defitelio 6.25 mg/kg was administered intravenously over 2 hours to subjects	peaked at the end of the infusion period and declined thereafter with a rapid clearance and most of samples were undetectable 3.5 hours after the start of the infusion. Pharmacokinetic modelling simulation analysis showed that Defitelio plasma concentrations do not accumulate upon multiple doses administration and with doses up to 4-fold the therapeutic dose. Volume of distribution is around 10 L and Defitelio is not bound to plasma proteins. <u>Elimination</u> 98% of Defitelio is excreted unchanged in the urine in the first 4 hours after the start of the infusion. The remaining 2% is excreted within 24 hours. <u>Special Populations</u>	

every 6 hours. Compared to healthy controls, subjects with renal impairment demonstrated 1.6 – and 1.4-fold increases in AUC and C_{max}, respectively and a half-life of about twice that of healthy subjects. The amount of defibrotide excreted in urine over 24hrs was about 5% of the total dose administered in those with renal impairment versus about 12% in healthy subjects. Almost all renal excretion occurs within the first 4 hours. Accumulation of defibrotide over 4 doses was not found. Difference in exposure is not considered clinically relevant and so dose adjustment is not advised for patients with renal impairment (see section 4.2). In a sub-study it was shown that haemodialysis did not remove defibrotide (see section 4.2) *Hepatic Impairment* No formal pharmacokinetic studies have been performed in hepatic impaired patients ~~special populations~~. Defitelio has been used in clinical trials in patients developing renal and hepatic impairment without dose adjustment with no major safety issues identified (see section 4.2).	No formal pharmacokinetic studies have been performed in special populations. Defitelio has been used in clinical trials in patients developing renal and hepatic impairment without dose adjustment with no major safety issues identified (see section 4.2).	