הודעה על החמרה (מידע בטיחות)

אושר – 10.16

תאריך: 26 ביוני 2016

שם תכשיר באנגלית: DIFOLTA Solution for Injection

מספר רישום: 149 31 33684

שם בעל הרישום: מעבדות רפא בע"מ

שינויים במידע בטיחותי ביחס לעלון המאושר בארץ מסומנים בצבע - צהוב=הוספה, ~~ירוק~~=מחיקה.

בעלון לרופא

פרק בעלון	טקסט חדש
Dosage and Administration	~~Difolta should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.~~ … For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended dose of Difolta is 15 mg/m^2. --- ***Monitoring*** … Monitor complete blood cell counts and severity of mucositis at baseline and weekly…. ***Dose Modification Recommendations*** … For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended starting dose of Difolta is 15 mg/m^2 with dose modification to 10 mg/m^2 for the toxicities specified in Tables 1, 2 and 3. **Table 1 Difolta Dose Modifications for Mucositis**

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤ Grade 1	Dose Upon Recovery in Patients with Severe Renal Impairment
Grade 2	Omit dose	Continue prior dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2	10 mg/m^2
Grade 3	Omit dose	20 mg/m^2	10 mg/m^2
Grade 4	Stop therapy		

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 Difolta Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart	Dose Upon Recovery in Patients with Severe Renal Impairment
Platelet < 50,000/mcL	1 week	Omit dose	Continue prior dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2	10 mg/m^2
	3 weeks	Stop therapy		
ANC 500-1,000/mcL and no fever	1 week	Omit dose	Continue prior dose	Continue prior dose
ANC 500-1,000/mcL with fever or ANC < 500/mcL	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support	10 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy		

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor

Table 3 Difolta Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade [a] on Day of Treatment	Action	Dose upon Recovery to ≤ Grade 2	Dose Upon Recovery in Patients with Severe Renal Impairment
Grade 3	Omit dose	20 mg/m^2	10 mg/m^2
Grade 4	Stop therapy		

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

…

…

Warnings and Precautions

5.2 Mucositis

Difolta can cause mucositis. Monitor for mucositis weekly and if ≥ Grade 2 mucositis is observed, omit and/or reduce the dose as outlined in Section 2.2 Table 1. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of mucositis [*see Dosage and Administration (2.1)(2.2) and Adverse Reactions (6.1)*].

…

5.4 Tumor Lysis Syndrome

Difolta can cause tumor lysis syndrome ~~has been reported in patients with lymphoma receiving Difolta.~~ (TLS). Monitor patients who are at increased risk of TLS and ~~treated for complications~~treat promptly.

5.5 Hepatic Toxicity

Difolta can cause hepatic toxicity and liver function test abnormalities. Persistent liver function test abnormalities may be indicators of hepatic toxicity and require dose

modification or discontinuation. Monitor liver function tests. Omit dose until recovery, adjust or discontinue therapy based on the severity of the hepatic toxicity [*see Dosage and Administration (2.2) and Use in Specific Populations (8.6)*]. **5.6 Risk of Increased Toxicity in the Presence of Impaired Renal Function** Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Serious adverse drug reactions including toxic epidermal necrolysis and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered Difolta therapy. Avoid Difolta use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk [*see Dosage and Administration (2.2), Adverse Reactions (6.2), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)*]. … ~~**5.7 Decreased Renal Function**~~ ~~Although Difolta has not been formally tested in patients with renal impairment, caution is advised when administering Difolta to patients with moderate to severe impairment. No data are available to safely guide the use of Difolta in patients with end stage renal disease undergoing dialysis and therefore its use in these patients is not recommended [*see Clinical Pharmacology (12.3)*].~~ ~~5.8 Elevated Liver Enzymes~~ ~~have been observed after Difolta administration~~	
…. **6.2 Post Marketing Experience** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. ***Dermatologic Reactions*** Toxic epidermal necrolysis, sometimes fatal, has been reported during post-marketing use of Difolta. Fatal cases have been reported following the first dose of Difolta, including when a reduced dose is given, and have been reported in patients with end-stage renal disease undergoing dialysis [*see Warnings and Precautions (5.3), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)*]. „	Adverse Reactions
… **8.5 Geriatric Use** In the PTCL efficacy study, 36% of patients (n = 40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (< 65 years compared with ≥ 65 years). Due to the contribution of renal excretion to overall clearance of pralatrexate (approximately 34%), age-related decline in renal function may lead to a reduction in clearance and a commensurate increase in plasma exposure. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of	Use in Specific Populations

concomitant disease or other drug therapy. Since elderly patients may be at higher risk, monitor more closely. Omit dose and subsequently adjust or discontinue therapy for exposure related toxicity [*see Dosage and Administration (2.2), Warnings and Precautions (5.5)(5.6), Use in Specific Populations (8.6)(8.7), and Clinical Pharmacology (12.3)*].

~~No dosage adjustment is required in elderly patients with normal renal function [*see Clinical Pharmacology (12.3)*]~~

8.6 Hepatic Impairment

The safety, efficacy and pharmacokinetics of Difolta have not been evaluated in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin > 1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN); and AST or ALT > 5 × ULN if documented hepatic involvement with lymphoma. Treatment with Difolta can cause hepatic toxicity and liver function test abnormalities [*see Dosage and Administration (2.2) and Warnings and Precautions (5.5)*].

8.7 Renal Impairment

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended dose of Difolta is 15 mg/m^2. For patients with mild to moderate renal impairment, dose reduction is not necessary.

Serious adverse drug reactions, including TEN and mucositis have been reported in patients with ESRD undergoing dialysis. Monitor patients for renal function and for systemic toxicity due to increased drug exposure and adjust dosing accordingly. Avoid the use of Difolta in patients with end stage renal disease undergoing dialysis unless the potential benefit justifies the potential risk [see Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.3, 5.6), Adverse Reactions (6.2), and Clinical Pharmacology (12.3)].

…

Pharmacokinetics in Specific Populations

Renal Impairment

In patients with cancer without renal impairment, approximately 34% of pralatrexate was excreted unchanged into urine following a single dose of 30 mg/m^2 administered as an intravenous push over 3-5 minutes. The pharmacokinetics of Difolta was studied in patients with varying degrees of renal impairment. In patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), the Difolta dose was 15 mg/m^2. Patients with normal renal clearance, mild renal impairment, and moderate renal impairment were all dosed with
30 mg/m^2. Mean exposures of the pralatrexate S-diastereomer and R-diastereomer were comparable across cohorts. The mean fraction of the administered dose excreted as unchanged diastereomers in urine (f_e) decreased with declining renal function. The non-renal clearance and volume of distribution of pralatrexate were unaffected by renal impairment [*see Use in Specific Populations (8.7)*].

,,,

Clinical Pharmacology

… **17.3 Mucositis** Inform patients of the signs and symptoms of mucositis. Instruct patients on ways to reduce the risk of its development, and/~~or~~ on ways to maintain nutrition and control discomfort from mucositis if it occurs. …	Patient Counseling Information