אוקטובר 2020

רופא/ה, רוקח/ת נכבד/ה,

עדכון עלון לרופא - **DIFOLTA, solution for injection**

מעבדות רפא מבקשת להביא לידיעתכם כי עודכן העלון לרופא של התכשיר.

מרכיב פעיל: 1 mL contains: 20 mg of pralatrexate

התוויה:

Difolta is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

כל השינויים הם שינויי נוסח. לא היו החמרות.

למידע המלא יש לעיין בעלון בשלמותו.

מצ"ב קישור לעלונים הסופיים.

העלון נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות (www.health.gov.il), וניתן גם לקבלו מודפס ע"י פניה לחברת מעבדות רפא בע"מ בטל' 02-5893939, RA@rafa.co.il.

בכבוד רב,

מגר' חנה הירש

רוקחת ממונה

FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT: DIFOLTA, solution for injection

COMPOSITION:

1 mL contains: 20 mg of pralatrexate (see section 3).

For full list of ingredients see section 11 ("Description").

1 INDICATIONS AND USAGE

Difolta is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

2.1 Important dosing information

Pretreatment Vitamin Supplementation

Folic Acid: Patients should take folic acid 1-1.25 mg orally once daily beginning 10 days before the first dose of Difolta. Continue folic acid during the full course of therapy and for 30 days after the last dose of Difolta [*see Warnings and Precautions (5.1) (5.2)*].

Vitamin B_{12}: Administer vitamin B_{12} 1 mg intramuscularly within 10 weeks prior to the first dose of Difolta and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with Difolta [*see Warnings and Precautions (5.1) (5.2)*].

Dosing and Administration

The recommended dose of Difolta is 30 mg/m^2 administered as an intravenous push over 3-5 minutes via the side port of a free flowing 0.9% Sodium Chloride Injection intravenous line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity. The calculated dose of Difolta should be aseptically withdrawn into a syringe for immediate use. Do not dilute Difolta.

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.

Difolta is a clear, yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

2.2 Monitoring and Dose Modifications for Adverse Reactions

Management of severe or intolerable adverse reactions may require dose omission, reduction, or discontinuation of Difolta therapy.

Monitoring

Monitor complete blood cell counts and severity of mucositis at baseline and weekly. Perform serum chemistry tests, including renal and hepatic function, prior to the start of the first and fourth dose of each cycle.

Recommended Dosage Modifications

Do not administer Difolta until:

- Mucositis should be Grade 1 or less.
- Platelet count should be 100,000/mcL or greater for first dose and 50,000/mcLor greater for all subsequent doses.
- Absolute neutrophil count (ANC) of 1,000/mcL or greater.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

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.

Dosage modification for adverse reactions are provided in Tables 1,2, and 3.

Table 1 Difolta Dosage 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] Based National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 Difolta Dose Modifications for Myelosuppression

Blood Count on Day of Treatment	**Duration of Toxicity**	**Action**	**Dose upon Restart**	**Dose Upon Recovery in Patients with Severe Renal Impairment**
Platelet less than 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 to 1,000/mcL and no fever	1 week	Omit dose	Continue prior dose	Continue prior dose
ANC 500 to 1,000/mcL with fever or ANC less than 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 Adverse reactions

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 NCI CTCAE, Version 3.0

2.3 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

Difolta is a hazardous drug. Follow applicable special handling and disposable procedures. If Difolta comes in contact with the skin, immediately and thoroughly wash with soap and water. If Difolta comes in contact with mucous membranes, flush thoroughly with water.

Aseptically withdraw the calculated dose from the appropriate number of vial(s) into a syringe for immediate use. Do not dilute Difolta

Administer undiluted Difolta intravenously over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection.

After withdrawal of dose, discard vial(s) including any unused portion.

3 DOSAGE FORMS AND STRENGTHS

Difolta is available as a clear yellow sterile solution in single-dose vials containing pralatrexate at a concentration of 20 mg/mL in the following presentations:

20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Difolta can cause myelosuppression, manifested by thrombocytopenia, neutropenia, and/or anemia.

Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of treatment-related myelosuppression *[see Dosage and Administration (2.1)]*

Monitor complete blood counts and omit and/or reduce the dose based on ANC and platelet count prior to each dose *[see Dosage and Administration (2.4)]*

5.2 Mucositis

Difolta can cause mucositis *[see Adverse Reactions (6.1)]*.

Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of mucositis [*see Dosage and Administration (2.1)]*.

Monitor for mucositis weekly and omit and/or reduce the dose for grade 2 or higher mucositis *[see Dosage and administration (2.4)]*.

5.3 Dermatologic Reactions
Difolta can cause severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (2.1% of 663 patients) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN) [*see Adverse Reactions (6.1, (6.2)*]. They may be progressive and increase in severity with further treatment and may involve skin and subcutaneous sites of known lymphoma.

Monitor closely for dermatologic reactions. Withhold or discontinue Difolta based on severity [*see Dosage and Administration (2.4)]*

5.4 Tumor Lysis Syndrome
Difolta can cause tumor lysis syndrome (TLS). Monitor patients who are at increased risk of TLS and treat promptly.

5.5 Hepatic Toxicity
Difolta can cause hepatic toxicity and liver function test abnormalities *[see Adverse Reactions (6.1)]*. 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)*].

5.6 Risk of Increased Toxicity with Renal Impairment
Patients with severe renal impairment(eGFR 15 to < 30mL/min/1.73 m^2 based on MDRD) may be at greater risk for increased exposure and adverse reactions Reduce Difolta dosage in patients with severe renal impaiment *see Dosage and Administration (2.2),*]

Serious adverse drug reactions including toxic epidermal necrolysis (TEN) 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 (ESRD) with or without dialysis. If the potential benefit of administration justifies the potential risk, monitor renal function and reduce the Difolta dose based on adverse reactions *[see Dosage and Administration (2.2)]*,

5.7 Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, Difolta can cause fetal harm when administered to a pregnant woman. Difolta was embryotoxic and fetotoxic in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Difolta and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Difolta and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression (Bone Marrow Suppression) *[see Warnings and Precautions (5.1)]*
- Mucositis *[see Warnings and Precautions (5.2)]*
- Dermatologic Reactions *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*

The most common adverse reactions observed in patients with peripheral T-cell lymphoma (PTCL) treated with Difolta were mucositis, thrombocytopenia, nausea, and fatigue.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of Difolta was evaluated in study PDX-008 *[see clinical studies (14)]*. Patients received Difolta 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range: 1day to-1.5 years).

The majority of patients (69%, n = 77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of Difolta. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Across clinical trials, deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients who received doses ranging from 30 mg/m^2 to 325 mg/m^2.

Twenty-three percent of patients (n = 25) discontinued treatment with Difolta due to adverse reactions. The most frequent adverse reactions reported as the reason for discontinuation of treatment were mucositis (6%) and thrombocytopenia (5%).

The most common adverse reactions (> 35%) were mucositis, thrombocytopenia, nausea, and fatigue.

Table 4 summarizes the adverse reactions in Study PDX-008.

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥ 10% of patients)

	N=111					
	Total		Grade 3		Grade 4	
Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
Any Adverse Event	111	100	48	43	34	31
Mucositis[a]	78	70	19	17	4	4
Thrombocytopenia[b]	45	41	15	14	21	19[b]
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal[c]	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

[a]Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts.

[b]Five patients with platelets < 10,000/mcL

[c]Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events
Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of Difolta. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all Difolta trials at doses ranging from 30 to 325 mg/m^2.

Discontinuations
Twenty-three percent of patients (n = 25) discontinued treatment with Difolta due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n = 7) and thrombocytopenia (5%, n = 5).

Dose Modifications
The target dose of Difolta was 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n = 77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

6.2 Post Marketing Experience

The following adverse reactions have been identified during postapproval use of Difolta.

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.

Reporting of suspected adverse reactions
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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

7 DRUG INTERACTIONS
Co-administration of Difolta with probenecid increased pralatrexate plasma concentrations [*see Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions.

Avoid coadministration with probenecid or nonsteroidal anti-inflamatory drugs. If coadministration is unavoidable, monitor for increased risk of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action [*see Clinical Pharmacology (12.1)*].

Difolta can cause fetal harm when administered to a pregnant woman. There are insufficient data on Difolta use in pregnant women to evaluate for a drug-associated risk. Difolta was embryotoxic and fetotoxic in rats and rabbits when administered during organogenesis at doses about 1.2% (0.012 times) of the clinical dose on a mg/m^2 basis. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pralatrexate was embryotoxic and fetotoxic in rats at intravenous doses of 0.06 mg/kg/day (0.36 mg/m^2/day or about 1.2% of the clinical dose on a mg/m^2 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, intravenous doses of 0.03 mg/kg/day (0.36 mg/m^2/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses.

8.2 Lactation

Risk Summary

There is no data on the presence of pralatrexate in human milk or its effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with FOLOTYN and for 1 week after the last dose.

8.3. Females and Males of Reproductive Potential

FOLOTYN can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiation of FOLOTYN.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with FOLOTYN and for 6 months following the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with FOLOTYN and for 3 months following the last dose.

8.4 Pediatric Use

The safety and effectiveness of Difolta in pediatric patients have not been established.

8.5 Geriatric Use
In the Study PDX-008 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 concomitant disease or another drug therapy. Since elderly patients may be at higher risk, monitor more closely. Omit dose and subsequently adjust or discontinue therapy for adverse reactions [*see Dosage and Administration (2.2),*

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
No dosage modification is recommended for patients with mild or moderate renal impairment (eGFR 30 mL/min to 59 mL/min/1.73 m^2 based on MDRD), For patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) , reduce the recommended dose of Difolta *[see Dosage and Administration (2.3)]*.

Serious adverse drug reactions, including TEN and mucositis, have been reported in patients with ESRD undergoing dialysis. Avoid the use of Difolta in patients with ESRD with or without dialysis. If the potential benefit of administration justifies the potential risk monitor renal function and reduce the Difolta dose based on adverse reactions [see Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.3, 5.6),].

10 OVERDOSAGE
No specific information is available on the treatment of overdosage of Difolta. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on Difolta's mechanism of action, consider the prompt administration of leucovorin.

11 DESCRIPTION
Pralatrexate is a dihydrofolate reductase inhibitor. Pralatrexate has the chemical name (2*S*)-2-[[4-[(1*RS*)-1-[(2, 4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid.
The molecular formula is $C_{23}H_{23}N_7O_5$ and the molecular weight is 477.48 g/mol.

Pralatrexate is a 1:1 racemic mixture of *S*- and *R*- diastereomers at the C10 position.

Pralatrexate is an off-white to yellow solid. It is soluble in aqueous solutions at pH 6.5 or higher. Pralatrexate is practically insoluble in chloroform and ethanol. The pKa values are 3.25, 4.76, and 6.17.

Difolta is supplied as a preservative-free, sterile, isotonic, non-pyrogenic clear yellow aqueous parenteral solution contained in a single-dose clear glass vial (Type I) for intravenous use. Each 1 mL of solution contains 20 mg of pralatrexate, sufficient sodium chloride to achieve an isotonic (280-300 mOsm) solution, and sufficient sodium hydroxide, and hydrochloric acid if needed, to adjust and maintain the pH at 7.5-8.5. Difolta is supplied as either 20 mg (1 mL) or 40 mg (2 mL) single-dose vials at a concentration of 20 mg/mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. It is also a competitive inhibitor for polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biological molecules the synthesis of which depends on single carbon transfer.

12.2 Pharmacodynamics

Pralatrexate exposure-response relationship and the time course of pharmacodynamics responses are unknown.

12.3 Pharmacokinetics

Pralatrexate is a racemic mixture of S- and R-diastereomers. The pharmacokinetics of pralatrexate at the recommended dosage of 30 mg/m^2 once weekly have been evaluated in 10 patients with PTCL. Pralatrexate total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increased proportionally over a dose range 30 to 325 mg/m^2 (10.8 times the approved recommended dosage). No accumulation of pralatrexate was observed.

Distribution

Steady-state volume of distribution of pralatrexate S- and R-diastereomers is 105 L and 37 respectively Protein binding of pralatrexate is approximately 67% in vitro.

Elimination

The total systemic clearance of pralatrexate diastereomers was 417 mL/min (*S*-diastereomer) and 191 mL/min (*R*-diastereomer). The terminal elimination half-life of pralatrexate was 12-18 hours (coefficient of variance [CV] = 62-120%).

Metabolism

Pralatrexate is not significantly metabolized by CYP450 isozymes or glucuronidases in vitro.

Excretion

Following a single dose of Difolta 30 mg/m^2, approximately 34% of the pralatrexate dose was excreted unchanged into urine. Following a radiolabeled pralatrexate dose, 39% (CV = 28%) of the dose was recovered in urine as unchanged pralatrexate and 34% (CV = 88%) in feces as unchanged pralatrexate and/or any metabolites. 10% (CV = 95%) of the dose was exhaled over 24 hours.

Pharmacokinetics in-Specific Populations

No clinically meaningful effect on the pharmacokinetics of pralatrexate was observed based on sex. The effect of hepatic impairment on the pharmacokinetics of pralatrexate has not been studied.

Patients with Renal Impairment

Following administration of a single dose of Difolta, mean exposures of the pralatrexate S-diastereomer and R-diastereomer were comparable in patients with mild to moderate (eGFR 30 to 59 mL/min/1.73 m^2 based on MDRD) renal impairment as compared with severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. The mean fraction of the administered dose excreted as unchanged diastereomers in urine (f_e) decreased with declining renal function *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Clinical Studies

Coadministration of probenecid (an inhibitor of multidrug resistance-associated protein 2 [MRP2] in vitro) resulted in delayed clearance of pralatrexate.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Pralatrexate does not induce or inhibit CYP enzymes.

Transporter Systems: Pralatrexate is a substrate for BCRP, MRP2, MRP3, and OATP1B3, but is not a substrate of P-gp, OATP1B1, OCT2, OAT1, or OAT3.

Pralatrexate inhibits MRP2 and MRP3, but does not inhibit P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3. MRP3 is a transporter that may affect the transport of etoposide and teniposide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies have not been performed with pralatrexate.

Mutagenesis
Pralatrexate did not cause mutations in the Ames test or the Chinese hamster ovary cell chromosome aberration assay. Nevertheless, these tests do not reliably predict genotoxicity for this class of compounds. Pralatrexate did not cause mutations in the mouse micronucleus assay.

Impairment of Fertility
No fertility studies have been performed.

14 CLINICAL STUDIES

Peripheral T-cell Lymphoma (PTCL)
The efficacy of Difolta was evaluated in study PDX-008, an open-label, single-arm, multi-center, international trial that enrolled patients with relapsed or refractory PTCL. One hundred and eleven patients received Difolta at 30 mg/m^2 intravenously over 3-5 minutes once weekly by for 6 weeks in 7-week cycles until disease progression or unacceptable toxicity. Of the 111 patients treated, 109 patients were evaluable for efficacy. Evaluable patients had histologically confirmed PTCL by independent central review using the Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification and relapsed or refractory disease after at least one prior treatment.

The major efficacy endpointoutcome measure was overall response rate (complete response, complete response unconfirmed, and partial response) as assessed by International Workshop Criteria (IWC an additional efficacy outcome measure was duration of response. Response assessments were scheduled at the end of cycle 1 and then every other cycle (every 14 weeks). Duration of response was measured from the first day of documented response to disease progression or death. Response and disease progression were evaluated by independent central review using the IWC.

The median age of treated patients was 59 years (range 21-85); 68% were male. 72% were white, 13% were black, 8% were Hispanic and 5% were Asian. Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (39%), 1 (44%), or 2 (17%). The median time from initial diagnosis to study entry was 1.3 years (range 24 days to 26.8 years).

The median number of prior systemic therapies was 3 (range 1-12). Approximately 24% of patients n = 27) did not have evidence of response to any previous therapy. Approximately 63% of patients (n = 70) did not have evidence of response to their most recent prior therapy before entering the study.

Table 5 Efficacy Results for Study PDX-008 per Independent Central Review (IWC)

	Evaluable Patients (N=109)			
	N (%)	**95% CI**	**Median Duration of Response**	**Range of Duration of Response**
Overall Response				
CR+CRu+PR	29 (27)	19, 36	287 days (9.4 months)	1-503 days
CR/CRu	9 (8)			
PR	20 (18)			
Responses ≥ 14 weeks				
CR+CRu+PR	13 (12)	7, 20	Not Reached	98-503 days
CR/CRu	7 (6)			
PR	6 (6)			

Fourteen patients went off treatment in cycle 1; 2 patients were unevaluable for response by IWC due to insufficient materials provided to central review.
CR = Complete Response, CRu = Complete Response unconfirmed, PR = Partial Response

The initial response assessment was scheduled at the end of cycle 1. Of the responders, 66% responded within cycle 1. The median time to first response was 45 days (range 37-349 days).

15 REFERENCES

1 OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/o tm/otm_vi/otm_vi_2.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Difolta is available in clear single-dose glass vials containing pralatrexate at a concentration of 20 mg/mL as a preservative-free, sterile, clear yellow solution individually packaged for intravenous use in the following presentations:

20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

Store refrigerated at 2-8°C in original carton to protect from light.

Difolta is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Each vial of Difolta is intended for single use only. Any unused drug remaining after injection must be discarded.

Rx only

REGISTRATION HOLDER:

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

Registration number:1493133684

MANUFACTURER: Anderson brecon (UK) Ltd.

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