Dyfixa® 200mg, 550mg Tablets
(Rifaximin)

ڈائفیکساء® گولیاں
(ریفاکسیمین) ۲۰۰ملی گرام ۵۵۰ملی گرام

Description:
Dyfixa Film coated tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The chemical name for rifaximin (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25 - pentahydroxy - 27 - methoxy - 2,4,11,16,20,22,24,26-octamethyl - 2,7 - (epoxypentadeca - [1,11,13] trienimino) benzofuro [4,5 - e]pyrido[1,2 - a] - benzimidazole - 1,15(2H)-dione,25-acetate. The empirical formula is C43H51N3O11 and its molecular weight is (g/mol)

Clinical Pharmacology:
Mechanism of Action:
Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependant RNA polymerase resulting in inhibition of bacterial RNA synthesis. Rifaximin has been shown to be active against the non invasive strains of E.Coli. For, HE it is thought to have an effect on the gastrointestinal flora.

Pharmacokinetics:
Absorption:
Travelers' Diarrhea:
Rifaximin has low intestinal permeability and low aqueous solubility therefore; it is poorly absorbed from the gastrointestinal tract, having a bioavailability of about only 0.4%. Systemic absorption of rifaximin (200 mg three times daily) was evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Dyfixa is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration.

Hepatic Encephalopathy:
After a single dose and multiple doses of rifaximin 550 mg in healthy subjects, the mean time to reach peak plasma concentrations was about an hour. The pharmacokinetic (PK) parameters were highly variable. The PK of rifaximin in patients with a history of HE was evaluated after administration of Dyfixa 550 mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure in patients with a history of HE (147 ngh/mL) was approximately 12-fold higher than that observed in healthy subjects following the same dosing regimen (12.3 ngh/mL).

Distribution:
80% to 90% in the gut. Elimination Half-life is ~6hours. Rifaximin is moderately bound to human plasma proteins. In vivo, the mean protein binding ratio is 67.5% in healthy subjects and 62% In patients with hepatic impairment when Dyfixa 550 mg was administered.

Metabolism:
Rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug. The enzymes responsible for metabolizing rifaximin are unknown.

Excretion:
Feces (~97% as unchanged drug); urine (<1%). In a separate study, rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of rifaximin.

Specific Populations:
Hepatic Impairment:
The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects. The mean AUC in patients with Child-Pugh Class C hepatic impairment was 2-fold higher than in patients with Child-Pugh Class A hepatic Impairment. No specific dose adjustments are recommended for patients with hepatic insufficiency.

Renal Impairment:
The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Drug Interactions:
The systemic drug interaction potential of rifaximin is low as it does not inhibit cytochrome P450 isoenzymes. In patients with normal function. rifaximin at the recommended dosing regimen is not expected to induce CYP3A4.It is known whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function. Due to the potential of severe disruption of gut flora with unknown consequences. Rifaximin should not be administered concomitantly with other rifamycins.

Dosage and Administration:
Dosage for Travelers' Diarrhea:
The recommended dose of Dyfixa is one 200 mg tablet taken orally three times a day for 3 days. Dyfixa can be administered orally, with or without food.

Dosage for Hepatic Encephalopathy:
The recommended dose of Dyfixa is one 550 mg tablet taken orally two times a day, up to 6 months, with or without food.

Contraindications:
Dyfixa is contraindicated in patients with a hypersensitivity to Rifaximin, or any of the excipient in Dyfixa. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema and anaphylaxis.

Warnings/Precautions:
Travelers' Diarrhea Not Caused by Escherichia coli:
Dyfixa was not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than Escherichia coli. Discontinue Dyfixa if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.
Dyfixa is not effective in cases of travelers' diarrhea due to Campylobacter jejuni. The effectiveness of Dyfixa in travelers' diarrhea caused by Shigella spp. and Salmonella spp. has not been proven. Dyfixa should not be used in patients where Campylobacter jejuni, Shigella spp., or Salmonella spp. may be suspected as causative pathogens.

Clostridium difficile-Associated Diarrhea:
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Dyfixa, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of C. difficile. It produces toxins A and B which contribute to the development of CDAD. Hyper toxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile and surgical evaluation should be instituted as clinically indicated.

Development of Drug Resistant Bacteria:
Prescribing Dyfixa for travelers' diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Severe (Child-Pugh C) Hepatic Impairment:
There is increased systemic exposure in patients with severe hepatic impairment. Caution should be exercised when administering Dyfixa to patients with severe hepatic impairment (Child-Pugh C).

Concomitant use with P-glycoprotein Inhibitors:
In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-glycoprotein inhibitors may further increase the systemic exposure to rifaximin.

Adverse Reactions:
Travelers' Diarrhea:
Flatulence, Headache, Abdominal Pain and distention, Rectal Tenesmus, Defecation Urgency, Nausea, Pyrexia, Vomiting, Chest pain, malaise, neck pain, muscle spasms, dizziness.

Hepatic Encephalopathy
Peripheral edema, Dizziness, Fatigue, Ascites, Muscle spasms, Pruritus, Abdominal pain, Abdominal distension, Anemia,cough,depression, insomnia, Nasopharyngitis, upper Abdominal pain , Arthralgia, Back pain, Constipation, Dyspnea, Pyrexia, Rash.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Pregnancy Category C:
There are no adequate and well controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity. Dyfixa tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Additional malformations were observed in fetal rabbits that included cleft palate, lumbar scoliosis, interventricular sepal defect and large atrium.

Nursing Mothers:
It is not known whether rifaximin is excreted in human milk or not. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Rifaximin a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
The safety and effectiveness of Dyfixa 200 mg in pediatric patients with travelers' diarrhea less than 12 years of age have not been established. The safety and effectiveness of Dyfixa 550 mg for HE have not been established in patients < 18 years of age.

Geriatric Use:
Clinical studies with rifaximin 200 mg for travelers' diarrhea did not include sufficient number of patients aging 65 and over to determine whether they respond differently than younger subjects. In the controlled trial with Dyfixa 550 mg for hepatic encephalopathy, 19.4% were 65 and over, while 2.3%. were 75 and over. No overall differences in safety of effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment:
The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Hepatic Impairment:
Following administration of Rifaximin 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally.

Over dosage:
No specific information is available on the treatment of over dosage with Dyfixa In clinical studies at doses higher than the recommended dose (> 600 mg/day for travelers' diarrhea of > 1100 mg/day for hepatic encephalopathy), adverse reactions were similar in subjects who received doses higher than the recommended dose and placebo. In the case of over dosage, discontinue Dyfixa and treat symptomatically, and institute supportive measures as required.

Storage:
Store Dyfixa Tablets at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Patient Counselling Information:
Persistent Diarrhea:
For those patients being treated for travelers' diarrhea, discontinue Dyfixa if diarrhea persists for more than 24 - 48 hours or worsens. Advise the patient to seek medical care for fever and/or blood in the stool.

Clostridium difficile-Associated Diarrhea:
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Dyfixa, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon which may lead to C. difficile. Patients can develop watery and bloody stools (with or without stomach cramp and fever) even as late as two or more months after having taken the last dose of the antibiotic

Dietary considerations
Dyfixa may be taken with or without food.

Keep out of reach of children

To be sold on prescription of a registered medical practitioner only

How Supplied:
- Dyfixa 200 is available in pack of 10's
- Dyfixa 550 is available in pack of 2 x 5's

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
خشک جگہ پر ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی دسترس سے دور رکھیں۔
سورج کی روشنی سے بچائیں۔

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