

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of fidaxomicin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Capsule shaped tablets of 14mm, white to off-white in colour, debossed with “FDX” on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIFICLIR is indicated for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in adult and paediatric patients aged 6 years and older (see section 4.2 and 5.1).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults

The recommended dose is 200 mg (one tablet) administered twice daily (once every 12 hours) for 10 days.

Special populations

Elderly population

No dose adjustment is considered necessary (see section 5.2).

Renal impairment

No dose adjustment is considered necessary. Due to the limited clinical data in this population, DIFICLIR should be used with caution in patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is considered necessary. Due to the limited clinical data in this population, DIFICLIR should be used with caution in patients with moderate to severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The recommended dose in paediatric patients weighing at least 12.5 kg is 200 mg administered twice daily (once every 12 hours) for 10 days using the film-coated tablets.

Method of administration

DIFICLIR is intended for oral use.

DIFICLIR must not be chewed or crushed and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions including severe angioedema have been reported (see section 4.8). If a severe allergic reaction occurs during treatment with DIFICLIR, the medicinal product should be discontinued and appropriate measures taken.

Some patients with hypersensitivity reactions reported a history of allergy to macrolides. Fidaxomicin should be used with caution in patients with a known macrolides allergy.

Renal and hepatic impairment

Due to limited clinical data, fidaxomicin should be used with caution in patients with severe renal impairment or moderate to severe hepatic impairment (see section 5.2).

Pseudomembranous colitis, fulminant or life threatening CDI

Due to limited clinical data, fidaxomicin should be used with caution in patients with pseudomembranous colitis, fulminant or life threatening CDI.

Co-administration of potent P-glycoprotein inhibitors

Co-administration of potent P-glycoprotein inhibitors such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended (see sections 4.5 and 5.2). In case fidaxomicin is administered concomitantly with potent P-glycoprotein inhibitors, caution is advised.

Paediatric population

Only one paediatric patient below 6 months of age has been exposed to fidaxomicin in clinical trials. Therefore, patients below 6 months of age should be treated with caution.

Testing for *C. difficile* colonization or toxin is not recommended in children younger than 1 year due to high rate of asymptomatic colonisation unless severe diarrhoea is present in infants with risk factors for stasis such as Hirschsprung disease, operated anal atresia or other severe motility disorders. Alternative aetiologies should always be sought and *C. difficile* enterocolitis be proven.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of P-gp inhibitors on fidaxomicin

Fidaxomicin is a substrate of P-gp. Co-administration of single doses of the P-gp inhibitor cyclosporine A and fidaxomicin in healthy volunteers, resulted in a 4- and 2-fold increase in fidaxomicin C_{max} and AUC, respectively and in a 9.5 and 4-fold increase in C_{max} and AUC, respectively, of the main active metabolite OP-1118. As the clinical relevance of this increase in exposure is unclear, co-administration of potent inhibitors of P-gp, such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone are not recommended (see sections 4.4 and 5.2).

Effect of fidaxomicin on P-gp substrates

Fidaxomicin may be a mild to moderate inhibitor of intestinal P-gp. Fidaxomicin (200 mg twice daily) had a small but not clinically relevant effect on digoxin exposure. However, a larger effect on P-gp substrates with lower bioavailability more sensitive to intestinal P-gp inhibition such as dabigatran etexilat cannot be excluded.

Effect of fidaxomicin on other transporters

Fidaxomicin does not have a clinically significant effect on the exposure of rosuvastatin, a substrate for the transporters OATP2B1 and BCRP. Co-administration of 200 mg fidaxomicin twice daily with a single dose of 10 mg rosuvastatin to healthy subjects did not have a clinically significant effect on the AUC_{inf} of rosuvastatin.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data available from the use of fidaxomicin in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of DIFICLIR during pregnancy.

Breast-feeding

It is unknown whether fidaxomicin and its metabolites are excreted in human milk. Although no effects on the breastfed newborns/infants are anticipated since the systemic exposure to fidaxomicin is low, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from DIFICLIR therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Fidaxomicin had no effects on fertility when evaluated in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

DIFICLIR has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are vomiting (1.2%), nausea (2.7%) and constipation (1.2%).

Tabulated summary of adverse reactions

Table 1 displays adverse reactions associated with twice daily administration of fidaxomicin in the treatment of *C. difficile* infection, reported in at least two patients, presented by system organ class.

The frequency of adverse reactions is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not

known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Summary of adverse reactions by MedDRA system organ class

MedDRA system organ class	Common	Uncommon	Frequency not known
Immune system disorders		rash, pruritus	hypersensitivity reactions (angioedema, dyspnea)
Metabolism and nutrition disorders		decreased appetite	
Nervous system disorders		dizziness, headache, dysgeusia	
Gastrointestinal disorders	vomiting, nausea, constipation	abdominal distention, flatulence, dry mouth	

Description of selected adverse reactions

Acute hypersensitivity reactions, such as angioedema and dyspnea, have been reported during post-marketing (see section 4.3 and 4.4).

Paediatric population

The safety and efficacy of fidaxomicin has been evaluated in 136 patients from birth to less than 18 years of age. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. In addition to the ADRs shown in table 1, two cases of urticaria were reported.

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/>

4.9 Overdose

No adverse reactions for acute overdose have been reported during clinical studies or from post-marketing data. However, the potential for adverse reactions cannot be ruled out and general supportive measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiarrheals, intestinal antiinflammatory/antiinfective agents, antibiotics, ATC code: A07AA12

Mechanism of action

Fidaxomicin is an antibiotic belonging to the macrocyclic class of antibacterials. Fidaxomicin is bactericidal and inhibits RNA synthesis by bacterial RNA polymerase. It interferes with RNA polymerase at a distinct site from that of rifamycins. Inhibition of the Clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E. coli* enzyme (1 µM vs. 20 µM), partly explaining the significant specificity of fidaxomicin activity. Fidaxomicin has been shown to inhibit *C. difficile* sporulation *in vitro*.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Fidaxomicin is a locally acting drug. As a topical agent, systemic PK/PD relationships cannot be established, however *in vitro* data show fidaxomicin to have time-dependent bactericidal activity and suggest time over MIC may be the parameter most predicative of clinical efficacy.

Breakpoints

Fidaxomicin is a topically acting drug that cannot be used to treat systemic infections; therefore the establishment of a clinical breakpoint is not relevant. The epidemiological cut-off value for fidaxomicin and *C. difficile*, distinguishing the wild-type population from isolates with acquired resistance traits, is ≥ 1.0 mg/L.

Antimicrobial spectrum

Fidaxomicin is a narrow spectrum antimicrobial drug with bactericidal activity against *C. difficile*. Fidaxomicin has an MIC₉₀ of 0.25 mg/L versus *C. difficile*, and its main metabolite, OP-1118, has an MIC₉₀ of 8 mg/L. Gram negative organisms are intrinsically not susceptible to fidaxomicin.

Effect on the intestinal flora

Studies have demonstrated that fidaxomicin treatment did not affect *Bacteroides* concentrations or other major components of the microbiota in the faeces of CDI patients.

Mechanism of resistance

There are no known transferable elements that confer resistance to fidaxomicin. Also no cross-resistance has been discovered with any other antibiotic class including β-lactams, macrolides, metronidazole, quinolones, rifampin, and vancomycin. Specific mutations of RNA polymerase are associated with reduced susceptibility to fidaxomicin.

Clinical efficacy in adults

In the pivotal clinical trials in adult patients the rate of recurrence in the 30 days following treatment was assessed as a secondary endpoint. The rate of recurrence (including relapses) was significantly lower with fidaxomicin (14.1% versus 26.0% with a 95% CI of [-16.8%, -6.8%]), however these trials were not prospectively designed to prove prevention of reinfection with a new strain.

Description of the patient population in clinical trials in adults

In the two pivotal clinical trials of patients with CDI, 47.9% (479/999) of patients (per protocol population) were ≥ 65 years of age and 27.5% (275/999) of patients were treated with concomitant antibiotics during the study period. Twenty-four percent of patients met at least one of the following three criteria at baseline for scoring severity: body temperature $>38.5^\circ\text{C}$, leukocyte count $>15,000$, or creatinine value ≥ 1.5 mg/dl. Patients with fulminant colitis and patients with multiple episodes (defined as more than one prior episode within the previous 3 months) of CDI were excluded from the studies.

Paediatric population

The safety and efficacy of fidaxomicin in paediatric patients from birth to less than 18 years of age was investigated in a multicentre, investigator-blind, randomised, parallel group study where 148 patients were randomised to either fidaxomicin or vancomycin in a 2:1 ratio. A total of 30, 49, 40 and 29 patients were randomised in the age groups of birth to < 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years, respectively. Confirmed clinical response 2 days after end of treatment was similar between the fidaxomicin and vancomycin group (77.6% vs 70.5% with a point difference of 7.5% and 95% CI for the difference of [-7.4%, 23.9%]). The rate of recurrence 30 days after end of treatment was numerically lower with fidaxomicin (11.8% vs 29.0%), but the rate difference is not statistically significant (point difference of -15.8% and 95% CI for the difference of [-34.5%, 0.5%]). Both treatments had a similar safety profile.

5.2 Pharmacokinetic properties

Absorption

The bioavailability in humans is unknown. In healthy adults, C_{max} is approximately 9.88 ng/ml and AUC_{0-t} is 69.5 ng-hr/ml following administration of 200 mg fidaxomicin, with a T_{max} of 1.75 hours. In CDI patients, average peak plasma levels of fidaxomicin and its main metabolite OP-1118 tend to be 2- to 6-fold higher than in healthy adults. There was very limited accumulation of fidaxomicin or OP-1118 in plasma following administration of 200 mg fidaxomicin every 12 hours for 10 days.

C_{max} for fidaxomicin and OP-1118 in plasma were 22% and 33% lower following a high fat meal vs fasting, but the extent of exposure (AUC_{0-t}) was equivalent.

Fidaxomicin and the metabolite OP-1118 are substrates of P-gp.

In vitro studies showed that fidaxomicin and the metabolite OP-1118 are inhibitors of the transporters BCRP, MRP2 and OATP2B1, but were not found to be substrates. Under conditions of clinical use, fidaxomicin has no clinically relevant effect on the exposure of rosuvastatin, a substrate for OATP2B1 and BCRP (see section 4.5). The clinical relevance of MRP2 inhibition is not yet known.

Distribution

The volume of distribution in humans is unknown, due to very limited absorption of fidaxomicin.

Biotransformation

No extensive analysis of metabolites in plasma has been performed, due to low levels of systemic absorption of fidaxomicin. A main metabolite, OP-1118, is formed through hydrolysis of the isobutyryl ester. *In vitro* metabolism studies showed that the formation of OP-1118 is not dependent on CYP450 enzymes. This metabolite also shows antimicrobial activity (see section 5.1).

Fidaxomicin does not induce or inhibit CYP450 enzymes *in vitro*.

Elimination

Following a single dose of 200 mg fidaxomicin, the majority of the administered dose (over 92%) was recovered in the stool as fidaxomicin or its metabolite OP-1118 (66%). The main elimination pathways of systemically available fidaxomicin have not been characterized. Elimination through urine is negligible (<1%). Only very low levels of OP-1118 and no fidaxomicin was detectable in human urine. The half life of fidaxomicin is approximately 8-10 h.

Special populations

Elderly

Plasma levels appear to be elevated in the elderly (age \geq 65 years). Fidaxomicin and OP-1118 levels were approximately 2 times higher in patients \geq 65 years compared to patients $<$ 65 years. This difference is not considered clinically relevant.

Paediatric population

After administration of film-coated tablets, the mean (SD) plasma levels in the paediatric patients from 6 to less than 18 years was 48.53 (69.85) ng/ml and 143.63 (286.31) ng/ml for fidaxomicin and its main metabolite OP-1118, respectively, at 1 to 5 hours postdose.

Inflammatory bowel disease

Data from an open label, single arm study in adult CDI patients with concomitant inflammatory bowel disease (IBD) indicated no major difference in plasma concentrations of fidaxomicin or its main metabolite OP-1118 in patients with IBD as compared with patients without IBD in other studies. The maximum fidaxomicin and OP-1118 plasma levels in CDI patients with concomitant IBD were within the range of levels found in CDI patients without IBD.

Hepatic impairment

Limited data from adult patients with an active history of chronic hepatic cirrhosis in the Phase 3 studies showed that median plasma levels of fidaxomicin and OP-1118 may be approximately 2- and 3-fold higher, respectively, than in non-cirrhotic patients.

Renal impairment

Limited data from adult patients suggest that there is no major difference in plasma concentration of fidaxomicin or OP-1118 between patients with reduced renal function (creatinine clearance $<$ 50 ml/min) and patients with normal renal function (creatinine clearance \geq 50 ml/min).

Gender, weight and race

Limited data suggest that gender, weight and race do not have any major influence on the plasma concentration of fidaxomicin or OP-1118.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and reproductive toxicity.

Reproductive and fertility parameters showed no statistically significant differences in rats treated with fidaxomicin at doses up to 6.3 mg/kg/day (intravenous).

No target organs for toxicity were observed in juvenile animals, and no important potential risks have been observed in the nonclinical studies that might be relevant for paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablets:

Microcrystalline cellulose
Pregelatinised starch (maize)
Hydroxypropyl cellulose
Butylated hydroxytoluene
Sodium starch glycolate
Magnesium stearate

Coating:

Polyvinyl alcohol

Titanium dioxide (E171)

Talc

Polyethylene glycol

Lecithin (soy)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

20 x 1 film-coated tablet in alu/alu perforated unit dose blisters.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Name of manufacture

Tillotts Pharma AG, Baslerstrasse 15, 4310 Rheinfelden, Switzerland.

8. Name of registration holder

Tradis Gat Ltd., 32 Shacham St., Petach Tikva,

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