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 14 mm, 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 film-coated tablets is indicated for the treatment of *Clostridioides difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in adult and paediatric patients with a body weight of at least 12.5 kg (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
Standard dosing
The recommended dose is 200 mg (one tablet) administered twice daily (once every 12 hours) for 10 days (see section 5.1).

DIFICLIR 40 mg/ml granules for oral suspension may be used in adult patients with difficulties in swallowing tablets.

Extended-pulsed dosing
Fidaxomicin 200 mg tablets administered twice daily for days 1-5 (no intake of a tablet on day 6) then once daily on alternate days for days 7-25 (see section 5.1).

If a dose has been forgotten, the missed dose should be taken as soon as possible or, if it's nearly time for the next dose, the tablet should be skipped altogether.

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, fidaxomicin 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, fidaxomicin 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 or the granules for oral suspension.

Reduced doses are recommended for patients with a body weight of less than 12.5 kg. See the SmPC of DIFICLIR 40 mg/ml granules for oral suspension.

Method of administration

DIFICLIR is intended for oral use.
The film-coated tablets should be administered whole with water.
They 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 fidaxomicin, 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 is 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 AUCinf 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 fidaxomicin 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 fidaxomicin 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 list 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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: Adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

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 MIC_{90} of 0.25 mg/L versus *C. difficile*, and its main metabolite, OP-1118, has an MIC_{90} 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

The efficacy of fidaxomicin was evaluated in two pivotal, randomised, double-blind Phase 3 studies (Study 003 and 004). Fidaxomicin was compared with orally administered vancomycin. The primary endpoint was clinical cure assessed after 12 days.

Non-inferiority of fidaxomicin compared with vancomycin was demonstrated in both studies (see Table 2)

Table 2 Combined results of studies 003 and 004

Per Protocol (PP)	**Fidaxomicin (200mg bid for 10 days)**	**Vancomycin (125mg qid for 10 days)**	**95% Confidence Interval***
Clinical Cure	91.9% (442/481 patients)	90.2% (467/518 patients)	(-1.8, 5.3)
modified Intent-to-Treat (mITT)	**Fidaxomicin (200mg bid)**	**Vancomycin (125mg qid)**	**95% Confidence Interval***
Clinical Cure	87.9% (474/539 patients)	86.2% (488/566 patients)	(-2.3, 5.7)

*for treatment difference

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 the pivotal 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°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.

Trial with the extended-pulse fidaxomicin dosing (EXTEND)
EXTEND was a randomised, open-label study that compared extended-pulse fidaxomicin dosing with orally administered vancomycin. The primary endpoint was sustained clinical cure 30 days after end of treatment (Day 55 for fidaxomicin, day 40 for vancomycin). The sustained clinical cure 30 days after end of treatment was significantly higher for fidaxomicin vs. vancomycin (see Table 3).

Table 3 Results of EXTEND study

modified Intent-to-Treat (mITT)	**Fidaxomicin (200mg bid for 5 days then 200mg every other day)**	**Vancomycin (125mg qid for 10 days)**	**95% Confidence Interval***
Clinical cure 30 days after end of treatment	70.1% (124/177 patients)	59.2% (106/179 patients)	(1.0, 20.7)

*for treatment difference

Description of the patient population in extended-pulse fidaxomicin dosing trial
The trial was conducted with adults aged 60 years and older. The median age of the patients was 75. 72% (257/356) received other antibiotics within the last 90 days. 36.5% had a severe infection.

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 ≥ 65 years). Fidaxomicin and OP-1118 levels were approximately 2 times higher in patients ≥ 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 ≥ 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/733/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 December 2011
Date of latest renewal: 22 August 2016

10. DATE OF REVISION OF THE TEXT

12 December 2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.