ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 the national reporting system listed in Appendix V.

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

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

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 40 mg/ml granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 40 mg of fidaxomicin when reconstituted with water.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.

White to yellowish white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIFICLIR granules for oral suspension is indicated for the treatment of *Clostridioides difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in adults and paediatric patients from birth to < 18 years of age (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 (5 ml) administered twice daily (once every 12 hours) for 10 days.

Special populations

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
For appropriate dosing in the paediatric population, granules for oral suspension or film-coated tablets may be used.

The recommended dose in paediatric patients weighing at least 12.5 kg is 200 mg (5 ml oral suspension) administered twice daily (once every 12 hours) for 10 days.

The recommended dose of the oral suspension in paediatric patients, by body weight, to be administered twice daily (once every 12 hours) for 10 days, is presented in the table below.

Table 1: Dosing instruction for the oral suspension

Weight band of patient	Mg per dose (every 12 hours)	Volume of fidaxomicin oral suspension (every 12 hours)
< 4.0 kg	40 mg	1 ml
4.0 - < 7.0 kg	80 mg	2 ml
7.0 - < 9.0 kg	120 mg	3 ml
9.0 - < 12.5 kg	160 mg	4 ml
≥ 12.5 kg	200 mg	5 ml

Method of administration

DIFICLIR is intended for oral use (by ingestion or via an enteral feeding tube using a syringe, if necessary).
The granules for oral suspension can be taken with or without food.

For instructions on reconstitution of the medicinal product before administration and administration via an enteral feeding tube, see section 6.6.

Instructions for use for the oral suspension:
The bottle should be taken from the refrigerator 15 minutes prior to administration and approximately 10 times gently shaken. Once reconstituted, the oral suspension should only be administered using the oral syringe and adaptor provided by the healthcare professional. The bottle should be stored in a refrigerator after each use.

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.

DIFICLIR contains sodium

DIFICLIR contains less than 1 mmol sodium (23 mg) per 5 ml suspension, that is to say essentially 'sodium-free'.

Paediatric population

Only one paediatric patient below 6 months of age and no patients with a body weight below 4 kg have been exposed to fidaxomicin in clinical trials. Therefore, fidaxomicin should be used with caution in these patients.

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.

Sodium benzoate content
This medicine contains 2.5 mg sodium benzoate (E 211) in each ml oral suspension. Sodium benzoate (E 211) may increase jaundice in newborn babies (up to 4 weeks old).

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 section 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 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 2 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 2: 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 2, 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 the national reporting system listed in Appendix V.

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

In the pivotal clinical trials in adult patients using the tablet formulation 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°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. After administration of fidaxomicin film-coated tablets 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

Paediatric population
After administration of the oral suspension, the mean (SD) plasma levels in the paediatric patients from birth to less than 18 years was 34.60 (57.79) ng/ml and 102.38 (245.19) ng/ml for fidaxomicin and its main metabolite OP-1118, respectively, at 1 to 5 hours postdose.

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.

Inflammatory bowel disease
Data from an open label, single arm study in adult CDI patients with concomitant inflammatory bowel disease (IBD) using the tablet formulation 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 using the tablet formulation 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 using the tablet formulation 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

Cellulose, microcrystalline
Sodium starch glycolate
Xanthan gum
Citric acid
Sodium citrate
Sodium benzoate (E211)
Sucralose
Mixed berry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The reconstituted suspension is stable for 12 days in a refrigerator (2°C – 8°C).

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
For storage conditions after reconstitution, see section 6.3.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber glass bottle with a polypropylene child-resistant cap in an aluminium pouch containing 7.7 g of granules for oral suspension.

6.6 Special precautions for disposal and other handling

DIFICLIR granules for oral suspension should be reconstituted by a pharmacist or other healthcare professional prior to dispensing to the patient. Patients or caregivers should not prepare the oral suspension at home.

Instructions for reconstitution:

1. Shake the glass bottle to ensure the granules move around freely and no caking of the granules has occurred.
2. Measure 105 ml of purified water and add to the glass bottle. Note that the stability of fidaxomicin granules suspended in mineral water, tap water, or other liquids has not been established.
3. Close the glass bottle and shake vigorously for at least 1 minute.
4. Verify that the resulting liquid has no remaining caked granules left at the bottom of the bottle or any lumps. If caked granules or any lumps are observed, shake the glass bottle vigorously again for at least 1 minute.
5. Let the bottle stand for 1 minute.
6. Verify if a homogenous suspension is obtained.
7. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf-life of the reconstituted suspension is 12 days).
8. Store the bottle at refrigerated temperature (2-8°C) before and during use.
9. Select an appropriate oral syringe and bottle adaptor suitable for dispensing liquid medicinal product to measure the correct dose.

After reconstitution, the suspension (110 ml) will appear as white to yellowish white.

An appropriate commercially available oral syringe and adaptor suitable for dispensing of liquid medicines should be selected by the healthcare professional in order to allow the patient or caregiver to measure the correct dose. The adaptor should be suitable for use in combination with the selected oral syringe and fits the bottle neck size, for example a press-in bottles adaptor (27 mm) or universal bottle adapter.

In case the treatment with fidaxomicin started in a hospital setting and the patient is discharged before the end of the treatment at the hospital, the patient should be provided with the oral suspension and a suitable oral syringe and adaptor. Patients or caregivers should not prepare the oral suspension at home.

Recommended oral syringe capacity for measuring the dose of the oral suspension is presented in the table below.

Table 3: Suggested oral syringe capacity for accurate dispensing

Prescribed dosing volume	Recommended oral syringe capacity
1 ml	1 ml oral syringe
2 – 5 ml	5 ml oral syringe

If possible, the graduation corresponding to the appropriate dose should be marked or highlighted (according to the dosing table in section 4.2) on the oral syringe.

Administration via an enteral feeding tube:

In case of administration using an enteral feeding tube, an appropriate commercially available tube should be selected by the healthcare professional. Enteral feeding tubes made of polyvinylchloride (PVC) and polyurethane (PUR) have been shown compatible with the oral suspension. The recommended enteral feeding tube size and flush volume of water are provided in the table below.

Table 4: Recommended enteral feeding tube size and flush volume

Recommended tube size (diameter)	Recommended flush volume*
4 Fr	at least 1 mL
5 Fr	at least 2 mL
6 – 7 Fr	at least 3 mL
8 Fr	at least 4 mL

* Based on tubes of 120 cm

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/1/11/733/005

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

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

DIFICLIR film-coated tablets
Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

DIFICLIR granules for oral suspension
Almac Pharma Services Limited
Seagoe Industrial Estate, Portadown, Craigavon,
BT63 5UA,
United Kingdom

Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 200 mg film-coated tablets
fidaxomicin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of fidaxomicin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 film-coated tablet.
20 x 1 film-coated tablet.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/733/003 100 x 1 film-coated tablet
EU/1/11/733/004 20 x 1 film-coated tablet

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

dificlir 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 200 mg film-coated tablets
fidaxomicin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Tillotts

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 40 mg/ml granules for oral suspension
fidaxomicin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the reconstituted suspension contains 40 mg fidaxomicin.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension
1 bottle contains 7.7 g granules or 110 ml oral suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use after reconstitution.
Shake well before use.
Use the oral syringe and adaptor provided by your pharmacist or healthcare professional.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted suspension can be stored for 12 days.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.
Reconstituted suspension: store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/733/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

dificlir 40 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

POUCH AND BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

DIFICLIR 40 mg/ml granules for oral suspension
fidaxomicin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the reconstituted suspension contains 40 mg fidaxomicin.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension
1 bottle contains 7.7 g granules or 110 ml oral suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use after reconstitution.
Shake well before use.
Use the oral syringe and adaptor provided by your pharmacist or healthcare professional

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted suspension can be stored for 12 days.
Expiry date of the reconstituted suspension:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.
Reconstituted suspension: store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Tillotts

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/733/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

DIFICLIR 200 mg film-coated tablets
fidaxomicin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DIFICLIR is and what it is used for

DIFICLIR is an antibiotic which contains the active substance fidaxomicin.

DIFICLIR film-coated tablets are used in adults, adolescents and children with a body weight of at least 12.5 kg to treat infections of the lining of the colon (large intestine) with certain bacteria called *Clostridioides difficile*. This serious illness can result in painful, severe diarrhoea. DIFICLIR works by killing the bacteria that cause the infection and helps to reduce the associated diarrhoea.

2. What you need to know before you take DIFICLIR

Do not take DIFICLIR
- If you are allergic to fidaxomicin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking DIFICLIR.

If you feel that you might have a severe allergic reaction such as trouble breathing (dyspnea), swelling of the face or throat (angioedema), severe rash, severe itching (pruritus) or severe hives (urticaria), stop taking DIFICLIR and seek medical advice urgently from your doctor, pharmacist or at your local hospital emergency department (see section 4).

If you are allergic to macrolides (a class of antibiotics), ask your doctor for advice before using this medicine. Your doctor will tell you whether this medicine is suitable for you.

If you have kidney or liver problems, ask your doctor for advice before using this medicine. Your doctor will tell you whether this medicine is suitable for you.

There are limited data available on the use of fidaxomicin in severe cases of the disease (e.g. pseudomembranous colitis). Your doctor will know whether your disease falls in the severe categories and will tell you whether this medicine is suitable for you.

Children and adolescents
Do not give this medicine to children with a body weight below 12.5 kg, because these children require a reduced dose. For appropriate dosing in these patients, DIFICLIR granules for oral suspension may be used.

Other medicines and DIFICLIR
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

DIFICLIR blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking DIFICLIR. Examples of such medicines are:
- cyclosporin (a medicine used to dampen down the body's immune reactions, used e.g. after an organ or bone marrow transplant, for psoriasis or eczema, or for rheumatoid arthritis or nephrotic syndrome)
- ketoconazole (a medicine used to treat fungal infections)
- erythromycin (a medicine used to treat ear, nose, throat, chest and skin infections)
- clarithromycin (a medicine used to treat chest infections, throat and sinus infections, skin and tissue infections and *Helicobacter pylori* infections associated with duodenal or stomach ulcer)
- verapamil (a medicine used to treat high blood pressure or to prevent chest pain attacks, or used following a heart attack to prevent another one)
- dronedarone and amiodarone (medicines used to control the heartbeat)
- dabigatran etexilat (a medicine used to prevent the formation of blood clots after hip or knee replacement surgery)

You should not use DIFICLIR in combination with one of these medicines, unless your doctor tells you otherwise. If you use one of these medicines, please ask your doctor for advice before taking this medicine.

Pregnancy and breast-feeding
You should not take DIFICLIR if you are pregnant, unless your doctor tells you otherwise.
This is because it is not known whether fidaxomicin can harm your baby.
If you are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether fidaxomicin passes into breast milk, but it is not expected to do so.
If you are breastfeeding ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
DIFICLIR is not expected to affect your ability to drive, use tools or machines.

DIFICLIR contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take DIFICLIR

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

The standard dosing for patients weighing at least 12.5 kg is one tablet (200 mg) twice daily (one tablet every 12 hours) for 10 days (see scheme 1 below).

It is possible that your doctor has prescribed an alternate dosing. The recommendation for an alternate

dosing is twice daily administration for days 1-5. Do not take a tablet on day 6, then once daily every other day for the days 7-25 (see also scheme 2 below).

Scheme 1 - Standard dosing

DAY	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Morning	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Evening	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Scheme 2 - Alternate dosing

DAY	1	2	3	4	5
Morning	200 mg	200 mg	200 mg	200 mg	200 mg
Evening	200 mg	200 mg	200 mg	200 mg	200 mg

DAY	6	7	8	9	10	11	12	13	14	15
	-	200 mg	-	200 mg	-	200 mg	-	200 mg	-	200 mg
DAY	16	17	18	19	20	21	22	23	24	25
	-	200 mg	-	200 mg	-	200 mg	-	200 mg	-	200 mg

200 mg - Dificlir 200 mg film-coated tablet

- No tablet

Swallow the tablets whole with a glass of water. You can take DIFICLIR before, during or after meals.

DIFICLIR granules for oral suspension should be used for patients with a body weight of less than 12.5 kg. This form of this medicine (oral suspension) may also be more suitable for patients above 12.5 kg; ask your doctor or pharmacist.

If you take more DIFICLIR than you should
If you have taken more tablets than you should have, talk to a doctor. Take the medicine pack with you so the doctor knows what you have taken.

If you forget to take DIFICLIR
Take the tablet as soon as you remember, unless it is time for the next dose. In that case, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking DIFICLIR
Do not stop taking DIFICLIR, unless your doctor has advised you to do so.
Keep taking this medicine until the course is finished, even if you feel better.
If you stop taking this medicine too soon, the infection may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A severe allergic reaction may occur, including trouble breathing (dyspnea), swelling of the face or throat (angioedema), severe rash or severe itching (pruritus) (see section 2). If such reaction occurs, stop taking DIFICLIR and seek medical advice urgently from your doctor, pharmacist or at your local hospital emergency department.

The most **common** side effects (may affect up to 1 in 10 people) are:
- vomiting
- nausea
- constipation.

Other possible side effects are the following:
Uncommon side effects (may affect up to 1 in 100 people)
– decreased appetite
– dizziness, headache
– dry mouth, altered taste (dysgeusia)
– bloated feeling, wind (flatulence)
– rash, itching (pruritus)

Not known side effects (frequency cannot be estimated from the available data)
– swelling of the face and throat (angioedema), trouble breathing (dyspnea)

Additional side effects in children and adolescents
– hives

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DIFICLIR

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What DIFICLIR contains
– The active substance is fidaxomicin. Each film-coated tablet contains 200 mg of fidaxomicin.
– The other ingredients are:
Tablet core: microcrystalline cellulose, pregelatinised starch, hydroxypropyl cellulose, butylated hydroxytoluene, sodium starch glycolate and magnesium stearate
Coating: polyvinyl alcohol, titanium dioxide (E171), talc, polyethylene glycol and lecithin (soy)

What DIFICLIR looks like and contents of the pack
DIFICLIR 200 mg film-coated tablets are capsule shaped tablets, white to off-white in colour, with "FDX" on one side and "200" on the other side.

DIFICLIR is available in:
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.

DIFICLIR is also available in the form of granules for oral suspension.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Tillotts Pharma GmbH
Warmbacher Strasse 80

79618 Rheinfelden
Germany

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

DIFICLIR 40 mg/ml granules for oral suspension
fidaxomicin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DIFICLIR is and what it is used for

DIFICLIR is an antibiotic which contains the active substance fidaxomicin.

DIFICLIR oral suspension is used in adults, adolescents and children from birth to less than 18 years to treat infections of the lining of the colon (large intestine) with certain bacteria called *Clostridioides difficile*. This serious illness can result in painful, severe diarrhoea. DIFICLIR works by killing the bacteria that cause the infection and helps to reduce the associated diarrhoea.

2. What you need to know before you take DIFICLIR

Do not take DIFICLIR
- If you are allergic to fidaxomicin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking DIFICLIR.

If you feel that you might have a severe allergic reaction such as trouble breathing (dyspnea), swelling of the face or throat (angioedema), severe rash, severe itching (pruritus) or severe hives (urticaria), stop taking DIFICLIR and seek medical advice urgently from your doctor, pharmacist or at your local hospital emergency department (see section 4).

If you are allergic to macrolides (a class of antibiotics), ask your doctor for advice before using this medicine. Your doctor will tell you whether this medicine is suitable for you.

If you have kidney or liver problems, ask your doctor for advice before using this medicine. Your doctor will tell you whether this medicine is suitable for you.

There are limited data available on the use of fidaxomicin in severe cases of the disease (e.g. pseudomembranous colitis). Your doctor will know whether your disease falls in the severe categories and will tell you whether this medicine is suitable for you.

Other medicines and DIFICLIR
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

DIFICLIR blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking DIFICLIR. Examples of such medicines are:
- cyclosporin (a medicine used to dampen down the body's immune reactions, used e.g. after an organ or bone marrow transplant, for psoriasis or eczema, or for rheumatoid arthritis or nephrotic syndrome)
- ketoconazole (a medicine used to treat fungal infections)
- erythromycin (a medicine used to treat ear, nose, throat, chest and skin infections)
- clarithromycin (a medicine used to treat chest infections, throat and sinus infections, skin and tissue infections and *Helicobacter pylori* infections associated with duodenal or stomach ulcer)
- verapamil (a medicine used to treat high blood pressure or to prevent chest pain attacks, or used following a heart attack to prevent another one)
- dronedarone and amiodarone (medicines used to control the heartbeat)
- dabigatran etexilat (a medicine used to prevent the formation of blood clots after hip or knee replacement surgery)

You should not use DIFICLIR in combination with one of these medicines, unless your doctor tells you otherwise. If you use one of these medicines, please ask your doctor for advice before taking this medicine.

Pregnancy and breast-feeding
You should not take DIFICLIR if you are pregnant, unless your doctor tells you otherwise.
This is because it is not known whether fidaxomicin can harm your baby.
If you are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether fidaxomicin passes into breast milk, but it is not expected to do so.
If you are breastfeeding ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
DIFICLIR is not expected to affect your ability to drive, use tools or machines.

DIFICLIR contains sodium benzoate (E211)
This medicine contains 2.5 mg sodium benzoate (E 211) in each ml oral suspension. Sodium benzoate (E 211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

DIFICLIR contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 5 ml suspension, that is to say essentially 'sodium-free'.

3. How to take DIFICLIR

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will determine your dose depending on your weight.

- The recommended dose for patients weighing at least 12.5 kg is 200 mg (5 ml oral suspension) administered twice daily (once every 12 hours) for 10 days. Another form of this medicine

(tablets) may be more suitable for adults and older children (e.g. adolescents); ask your doctor or pharmacist.

The recommended dose for children by body weight is as follows:

Weight band of patient	**Mg per dose (every 12 hours)**	**Volume of fidaxomicin oral suspension (every 12 hours)**
< 4.0 kg	40 mg	1 ml
4.0 - < 7.0 kg	80 mg	2 ml
7.0 - < 9.0 kg	120 mg	3 ml
9.0 - < 12.5 kg	160 mg	4 ml
≥ 12.5 kg	200 mg	5 ml

You can take DIFICLIR before, during or after meals.

How to take the DIFICLIR dose using an oral syringe

Your pharmacist or heatlthcare professional will prepare DIFICLIR oral suspension before giving it to you. If the product is not provided to you as a suspension, please contact your pharmacist or healthcare professional.

Instructions for use:
Use the oral syringe and adaptor provided by the pharmacist or healthcare professional to make sure you measure the right amount. If an oral syringe and adaptor has not been provided to you, please contact your pharmacist or healthcare professional.
Your pharmacist will advise you how to measure the medicine using the oral syringe. Please see instructions below before using DIFICLIR suspension.

1. Take the bottle from the refrigerator 15 minutes prior to administration.
2. After 15 minutes, shake the bottle gently 10 times and let the bottle stand for 1 minute.
3. Verify if the liquid is smooth and not lumpy (i.e. homogenous).
4. Remove the cap and attach the adaptor to the bottle according to the instructions by your pharmacist or healthcare professional.
5. Insert the tip of the oral syringe into the adaptor until it is firmly in place.
6. Invert the bottle 3 times and turn the bottle upside down, so the syringe is on the bottom.
7. Pull back the plunger of the oral syringe to withdraw the amount prescribed by your doctor from the inverted bottle.
8. Leave the syringe in place and turn the bottle upright, ensuring the plunger does not move. Gently remove the syringe from the adaptor and confirm the appropriate dose has been measured.
9. Slowly dispense the oral suspension directly into the patient’s mouth until all of the liquid medicine is given.
10. If you have been given a press-in adaptor, leave the bottle adaptor in the neck of the bottle or follow the instructions by your pharmacist or healthcare professional.
11. After administration, store the remaining suspension in a refigerator.
12. To allow reuse of the oral syringe, flush the syringe with warm drinking water (3 times minimally) or until clear water comes out of the syringe. Dry external surfaces and internal surfaces as much as possible. Leave to dry until further use.

If you started using this product in a hospital, your pharmacist or healthcare professional will provide you with the suspension, oral syringe and adaptor at your discharge.

If you take more DIFICLIR than you should
If you have taken more of the oral suspension than you should have, talk to a doctor. Take the medicine pack with you so the doctor knows what you have taken.

If you forget to take DIFICLIR
Take the oral suspension as soon as you remember, unless it is time for the next dose. In that case, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking DIFICLIR
Do not stop taking DIFICLIR, unless your doctor has advised you to do so.
Keep taking this medicine until the course is finished, even if you feel better.
If you stop taking this medicine too soon, the infection may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A severe allergic reaction may occur, including trouble breathing (dyspnea), swelling of the face or throat (angioedema), severe rash or severe itching (pruritus) (see section 2). If such reaction occurs, stop taking DIFICLIR and seek medical advice urgently from your doctor, pharmacist or at your local hospital emergency department.

The most **common** side effects (may affect up to 1 in 10 people) are:
– vomiting
– nausea
– constipation.

Other possible side effects are the following:
Uncommon side effects (may affect up to 1 in 100 people)
– decreased appetite
– dizziness, headache
– dry mouth, altered taste (dysgeusia)
– bloated feeling, wind (flatulence)
– rash, itching (pruritus)

Not known side effects (frequency cannot be estimated from the available data)
– swelling of the face and throat (angioedema), trouble breathing (dyspnea)

Additional side effects in children and adolescents
– hives

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DIFICLIR

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

DIFICLIR will be supplied to you as a suspension, which can be stored for up to 12 days. Store in a refrigerator (2°C - 8°C). Do not use the suspension after the expiry date which is written on the bottle label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What DIFICLIR contains
- The active substance is fidaxomicin.
- The other ingredients are: microcrystalline cellulose, sodium starch glycolate, xanthan gum, citric acid, sodium citrate, sodium benzoate (see section 2), sucralose and mixed berry flavour

What DIFICLIR looks like and contents of the pack
DIFICLIR is presented in an amber glass bottle as white to yellowish white granules for oral suspension. DIFICLIR will be supplied to you as a suspension by your pharmacist or healthcare professional, which will appear as white to yellowish white suspension.
The pack does not contain the oral syringe and adaptor for use with this product. These will be provided to you by your pharmacist or other healthcare professional.

DIFICLIR is also available in the form of film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Tillotts Pharma GmbH
Warmbacher Strasse 80
79618 Rheinfelden
Germany

Manufacturer
Almac Pharma Services Limited
Seagoe Industrial Estate, Portadown, Craigavon,
BT63 5UA,
United Kingdom

Tillotts Pharma GmbH
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Germany

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The following information is intended for healthcare professionals only:

Instructions for reconstitution:
1. Shake the glass bottle to ensure the granules move around freely and no caking of the granules has occurred.

2. Measure 105 ml of purified water and add to the glass bottle. Note that the stability of fidaxomicin granules suspended in mineral water, tap water, or other liquids has not been established.
3. Close the glass bottle and shake vigorously for at least 1 minute.
4. Verify that the resulting liquid has no remaining caked granules left at the bottom of the bottle or any lumps. If caked granules or any lumps are observed, shake the glass bottle vigorously again for at least 1 minute.
5. Let the bottle stand for 1 minute.
6. Verify if a homogenous suspension is obtained.
7. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf-life of the reconstituted suspension is 12 days).
8. Store the bottle at refrigerated temperature (2-8°C) before and during use.
9. Select an appropriate oral syringe and bottle adaptor suitable for dispensing liquid medicinal product to measure the correct dose.

After reconstitution, the suspension (110 ml) will appear as white to yellowish white.

An appropriate commercially available oral syringe and adaptor suitable for dispensing of liquid medicines should be selected by the healthcare professional in order to allow the patient or caregiver to measure the correct dose. The adaptor should be suitable for use in combination with the selected oral syringe and fits the bottle neck size, for example a press-in bottles adaptor (27 mm) or universal bottle adapter.

In case the treatment with fidaxomicin started in a hospital setting and the patient is discharged before the end of the treatment at the hospital, the patient should be provided with the oral suspension and a suitable oral syringe and adaptor. Patients or caregivers should not prepare the oral suspension at home.

Recommended oral syringe capacity for measuring the dose of the oral suspension is presented in the table below.

Suggested oral syringe capacity for accurate dispensing

Prescribed dosing volume	Recommended oral syringe capacity
1 ml	1 ml oral syringe
2 – 5 ml	5 ml oral syringe

If possible, the graduation corresponding to the appropriate dose should be marked or highlighted (according to the dosing table in section 3) on the oral syringe.

Administration via an enteral feeding tube:
In case of administration using an enteral feeding tube, an appropriate commercially available tube should be selected by the healthcare professional. Enteral feeding tubes made of polyvinylchloride (PVC) and polyurethane (PUR) have been shown compatible with the oral suspension. The recommended enteral feeding tube size and flush volume of water are provided in the table below.

Recommended enteral feeding tube size and flush volume

Recommended tube size (diameter)	Recommended flush volume*
4 Fr	at least 1 mL
5 Fr	at least 2 mL
6 – 7 Fr	at least 3 mL
8 Fr	at least 4 mL

* Based on tubes of 120 cm