SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FIDAXOMICIN 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

FIDAXOMICIN 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

Standard dosing
The recommended dose is 200 mg (5 ml) administered twice daily (once every 12 hours) for 10 days (see section 5.1).

Extended-pulsed dosing

Fidaxomicin 40 mg/ml granules for oral suspension (5 ml) administered twice daily for days 1-5 (no intake of suspension 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

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
FIDAXOMICIN 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.

FIDAXOMICIN contains sodium
FIDAXOMICIN 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

FIDAXOMICIN 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 **Error! Reference source not found.**).

Table 3 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 **Error! Reference source**

not found.).

Table 4 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. 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 27 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

FIDAXOMICIN 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 27 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 5: 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 6: 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 UK Ltd
Wellingore Hall, Wellingore
Lincolnshire, LN5 0HX, UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 36633/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/02/2021

10 DATE OF REVISION OF THE TEXT

18/04/2024