PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FIDICID 200 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg fidaxomicin.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off-white film-coated modified capsule shaped tablet debossed with “FDX” on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FIDICID 200 mg is indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) (see section 5.1).

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

4.2 Posology and method of administration

Posology

Adults and elderly (≥ 65 years of age)

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

Special populations

Renal impairment

No dose adjustment is considered necessary. Due to limited clinical data in this population, FIDICID 200 mg should be used with caution in patients with severe renal impairment (< 30 ml/min eGFR) (see section 4.4 and 5.2).

Hepatic impairment

No dose adjustment is considered necessary. Due to the limited clinical data in this population, FIDICID 200 mg should be used with caution in patients with moderate (serum total bilirubin 34 – 50 μmol/L) to severe hepatic impairment (serum total bilirubin > 50 μmol/L) (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of FIDICID 200 mg in children aged below 18 years has not yet been established. No data are available.

Method of administration

FIDICID 200 mg is intended for oral administration.

FIDICID 200 mg can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, fidaxomicin 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 FIDICID 200 mg, the medicine should be discontinued, and appropriate measures taken.

Some patients with hypersensitivity reactions reported a history of allergy to macrolides. Fidaxomicin, such as contained in FIDICID 200 mg should be used with caution in patients with a known macrolide (e.g. erythromycin or azithromycin) allergy.

Renal and Hepatic Impairment:

Due to limited clinical data FIDICID 200 mg should be used with caution in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) or moderate to severe hepatic impairment (serum total bilirubin 34 – > 50 µmol/L) (see section 5.2).

Pseudomembranous colitis, fulminant or life threatening CDI

Due to limited clinical data, FIDICID 200 mg 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 ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended (see section 4.5).

In case fidaxomicin, such as contained in FIDICID 200 mg is administered concomitantly with potent P-glycoprotein inhibitors, caution is advised.

4.5 Interaction with other medicines and other forms of interaction

Effect of P-gp inhibitors on FIDICID 200 mg

Fidaxomicin (the active ingredient in FIDICID 200 mg) is a substrate of P-glycoprotein (P-gp). Co-administration of single doses of the P-gp inhibitor ciclosporin A and FIDICID 200 mg in healthy

volunteers resulted in a 4- and 2-fold increase in fidaxomicin, such as contained in FIDICID 200 mg, C_{max} and AUC, respectively and 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 ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended (see section 4.4).

Effect of FIDICID 200 mg on P-gp substrates

When digoxin, a P-gp substrate, was co-administered with FIDICID (200 mg twice daily) in healthy volunteers, digoxin C_{max} increased by 14 % and AUC by 12 %.

Fidaxomicin such as contained in FIDICID 200 mg 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, a P-gp substrate, 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.

P450 (CYP) enzymes

FIDICID 200 mg is not metabolised by human cytochrome P450 (CYP) enzymes and does not induce or inhibit these enzymes *in vitro*. *In vivo* in healthy volunteers, FIDICID 200 mg did not have a clinically relevant effect on the CYP2C9 substrates warfarin, CYP3A4 substrate midazolam, and CYP2C19 substrate omeprazole. Based on these results, no dose adjustment of either medicine is warranted when FIDICID 200 mg is co-administered with CYP substrate compounds.

Effect of FIDICID 200 mg on other transporters

FIDICID 200 mg does not have a clinically significant effect on the exposure of a single dose of rosuvastatin, a substrate for the transporters OATP2B1 and BCRP. Co-administration of FIDICID 200 mg 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy in pregnancy has not been established.

Lactation

The safety and efficacy in lactation has not been established.

Fertility

Non-clinical data revealed no special hazard for humans based on conventional studies of reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

FIDICID 200 mg causes dizziness (see section 4.8). This may influence the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

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 (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**	**Frequency not known**
Immune system disorders		rash, pruritus	hypersensitivity reactions (angioedema, dyspnoea)
Metabolism and nutrition disorders		decreased appetite	
Nervous system disorders		dizziness, headache, dysgeusia	
Gastrointestinal disorders	vomiting, nausea, constipation	abdominal distention, flatulence, dry mouth	
Hepatobiliary disorders	increased alanine aminotransferase		

c. Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects will be exaggerated and exacerbated. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.20.3 Other antibacterial agents

Pharmacotherapeutic group: Intestinal anti-infectives, 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 *Clostridium difficile* sporulation *in vitro*.

Pharmacokinetic/ Pharmacodynamic (PK/PD) relationship

Fidaxomicin is a locally acting medicine. 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 predictive of clinical efficacy.

Breakpoints

Fidaxomicin is a topically acting medicine 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 *Clostridium 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 medicine with bactericidal activity against *Clostridium difficile* infections. 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 *Clostridium difficile* infected 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.

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 *Clostridium difficile* infected 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 characterised. 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

In controlled trials of patients treated with fidaxomicin 200 mg twice daily for 10 days, mean and median values of fidaxomicin and OP-1118 plasma concentrations within the T_{max} window (1 – 5 hours) were approximately 2 – 4 fold higher in elderly patients (≥ 65 years of age) versus non-elderly patients (< 65 years of age). Despite greater exposures in elderly patients, fidaxomicin and OP-1118 plasma concentrations remained in the ng/mL range. This difference is not considered to be clinically relevant.

Gender, race and weight

Plasma concentrations of fidaxomicin and OP-1118 within the T_{max} window (1-5 hours) did not vary by gender, race or weight in patients treated with fidaxomicin 200 mg twice daily for 10 days from controlled trials. No dose adjustment is recommended based on these parameters.

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). There is only limited scientific data available in patients with severe renal function.

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. There is no scientific data available in patients with severe hepatic function (see section 4.4).

Inflammatory bowel disease

Data from an open label, single arm study in 25 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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablets:

Microcrystalline cellulose

Pregelatinised starch

Hydroxypropyl cellulose

Butylated hydroxytoluene

Sodium starch glycolate

Magnesium stearate

Coating:

Polyvinyl alcohol

Titanium dioxide

Talc

Polyethylene glycol

Lecithin (soy)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

20 x 1 film-coated tablet in alu/alu perforated unit dose blisters (10 film-coated tablets per blister card;

2 blister cards per carton).

6.6 Special precautions for disposal and or other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

47/20.3/1137

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 November 2017

10. DATE OF REVISION OF THE TEXT

18 March 2025