SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

FIDICID 200 mg film-coated tablet

COMPOSITION

Active ingredient: Each tablet contains 200 mg fidaxomicin.

Inactive ingredients:

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).

PHARMACOLOGICAL CLASSIFICATION

A.20.3 Other antibacterial agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

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.

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 Pharmacodynamic Properties).

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

Geriatrics

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

In controlled trials of patients treated with fidaxomicin 200 mg twice daily for 10 days, plasma concentrations of fidaxomicin and OP-1118 within the T_{max} window (1-5 hours) did not vary by severity of renal impairment (based on creatinine clearance) between mild (51-79 mL/min), moderate (31-50 mL/min), and severe (≤30 mL/min) categories. No dose adjustment is recommended based on renal function.

Hepatic impairment

The impact of hepatic impairment on the pharmacokinetics of fidaxomicin has not been evaluated. Because fidaxomicin and OP-1118 do not appear to undergo significant hepatic metabolism, elimination of fidaxomicin and OP-1118 is not expected to be significantly affected by hepatic impairment. Limited data from 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.

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.

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 Pharmacodynamic Properties).

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS and SPECIAL PRECAUTIONS

Renal and Hepatic Impairment:

There are limited clinical data in patients with severe renal impairment and in those with severe hepatic impairment but no dose adjustment is considered necessary. It is known that patients with severe hepatic impairment may have increased exposure to FIDICID 200 mg. For these reasons, FIDICID 200 mg should be used with caution in such patients (see Pharmacokinetic Properties in Special Populations).

Inflammatory bowel disease and pseudomembranous colitis:

There are no data in patients with concomitant inflammatory bowel diseases and very little data in patients with pseudomembranous colitis. FIDICID 200 mg should be used with caution in these patients.

Effects on ability to drive and use machines

FIDICID 200 mg causes dizziness. This may influence the ability to drive and use machines.

INTERACTIONS

In vitro, FIDICID 200 mg is not metabolised by human cytochrome P450 (CYP) enzymes and does not induce or inhibit these enzymes *in vitro*. *In vitro*, fidaxomicin (the active ingredient in FIDICID 200 mg) and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract. Fidaxomicin is also an inhibitor of P-gp *in vitro*. 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 C_{max} and AUC, respectively and a 9.5- and 4-fold increase in C_{max} and AUC of the main active metabolite OP-1118.

P-gp inhibitors and substrates

P-gp inhibitors

Ciclosporin is an inhibitor of multiple transporters, including P-gp. When ciclosporin was co-administered with FIDICID 200 mg in healthy adult volunteers, plasma concentrations of fidaxomicin and OP-1118 were significantly increased but remained in the ng/mL range. Concentrations of fidaxomicin and OP-1118 may also be decreased at the site of action (i.e., gastrointestinal tract) via P-gp inhibition; however, in controlled clinical trials in patients with CDAD, P-gp inhibitor use at some time during the study had no attributable effect on safety or treatment outcome of FIDICID-treated patients. Based on these results, FIDICID 200 mg may be co-administered with P-gp inhibitors and no dose adjustment is recommended.

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 %. This effect of FIDICID 200 mg on digoxin exposure is not considered clinically relevant. 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.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

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.

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.

Renal impairment

No dose adjustment is considered necessary. Limited data in this population is available (see sections Warnings and Special Precautions and Pharmacokinetic Properties).

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 severe hepatic impairment (see sections Warnings and Special Precautions and Pharmacokinetic Properties).

Method of administration

FIDICID 200 mg is intended for oral administration.

FIDICID 200 mg can be taken with or without food.

SIDE EFFECTS

The safety profile of FIDICID 200 mg is based on data from 564 patients with *Clostridium difficile* infections treated with fidaxomicin in Phase 3 studies.

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

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.

MedDRA System Organ Class	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**
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	

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

IDENTIFICATION

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

PRESENTATION

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).

STORAGE INSTRUCTIONS

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

47/20.3/1137

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.
100 Sovereign Drive
Route 21, Corporate Park
Nellmapius Drive, Irene
Pretoria
0157

DATE OF PUBLICATION OF THE PACKAGE INSERT

23 Nov 2017