Fidaxomicin (Dificid – Optimer Pharmaceuticals Canada, Inc.): a new antibacterial agent for Clostridium difficile infection

BACKGROUND

Clostridium difficile infection (CDI) is a major cause of intestinal disease, especially among hospitalized patients exposed to antibiotics.1 Recent increases in the incidence and severity of CDI have been reported, related in part to increased use and misuse of antibiotics, and also to the emergence of a hypervirulent strain of C. difficile (NAP1/BI/027 strain) that produces higher levels of toxins than historic strains.1,2 The burden of illness associated with CDI is substantial, including prolonged hospital stays, excess health care expenditures, and increased morbidity and mortality.1,2

C. difficile is an anaerobic, Gram-positive, toxin-producing bacterium that is prevalent in nature.1,3 It exists in both vegetative and spore forms; in its spore form, C. difficile can survive harsh environments and common sterilization techniques.2 Spores are also resistant to antibiotics; hence, they can remain in the gastrointestinal tract and may contribute to recurrent disease after treatment and eradication of vegetative C. difficile.2 The principal mode of bacterial transmission resulting in CDI is person-to-person spread by the fecal-oral route.6,7 After bacterial ingestion and colonization of the large intestine, spores convert to vegetative bacteria that divide and produce the toxins responsible for clinical disease.2,7

Previously available treatments for CDI have been inadequate in some clinical scenarios. Fidaxomicin is a novel antibacterial agent that was recently approved by Health Canada for CDI. It is the first new treatment approved for the disease in over 20 years.8

INDICATIONS

Fidaxomicin is approved for the treatment of CDI in adults (≥18 years of age).9

PHARMACOLOGY & MICROBIOLOGIC ACTIVITY

Fidaxomicin is a narrow-spectrum macrocyclic antibiotic that inhibits bacterial transcription by binding to RNA polymerase.1,3 The drug has activity primarily against gram-positive aerobes and anaerobes, and is bactericidal against C. difficile; it lacks significant activity against gram-negative organisms, including Bacteroides species.1,4 While fidaxomicin does have activity against staphylococci and enterococci, its use may contribute less to the development of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) than some other commonly used agents.3,4

Fidaxomicin was shown to have a postantibiotic effect† ranging from 5.5 to 12.5 hours, which likely contributes to the drug’s efficacy.3 The agent has also been shown to inhibit C. difficile sporulation and toxin production in vitro.9

PHARMACOKINETICS

Systemic absorption of fidaxomicin is minimal following oral administration.3 Distribution is mainly confined to the gastrointestinal tract, and fecal concentrations in the colon exceed the MIC90 of C. difficile throughout the dosing interval.3 The drug is partially transformed by hydrolysis in the stomach and/or intestines to OP-1118, a microbiologically active metabolite with activity that is 8–16-fold lower than that of the parent compound.3,11 Excretion occurs primarily in feces, with negligible (<1%) urinary elimination.9 The half-life of fidaxomicin is approximately 8–10 hours.9

Efficacy

The characteristics and selected results of the pivotal trials12,13 evaluating fidaxomicin in patients with CDI are summarized in Table 1. In both trials, fidaxomicin was found to be non-inferior to...
vancomycin for the primary endpoint of clinical cure (see Table 1 footnotes for definition), and results were consistent in subgroup analyses looking at age (<65 years versus ≥65 years), hospital status (inpatient vs. outpatient), history of previous CDI, C. difficile strain (NAP1/B1/027 vs. non-NAP1/B1/027), and disease severity. For the secondary endpoints of recurrence and sustained response (see Table 1 footnotes for definitions), fidaxomicin was statistically superior to vancomycin in the overall study populations. When recurrence was analyzed by subgroup, fidaxomicin resulted in numerically lower rates than vancomycin in all instances in one study. However, the other study reported numerically higher (but statistically non-significant) recurrence rates for fidaxomicin than vancomycin in patients with the NAP1/B1/027 C. difficile strain (modified intent-to-treat population: 27.1% [16/59] vs. 20.9% [14/67], p=0.42; per-protocol population: 24.4% [11/45] vs. 23.6% [13/55], p=0.93).

<p>| Table 1 – Summary of pivotal fidaxomicin studies in CDI |</p>
<table>
<thead>
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<th>Study &amp; Design</th>
<th>Participants*</th>
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<tr>
<td>Cornely et al.</td>
<td>Patients (n=535) ≥16 years with acute, toxin-positive CDI and &gt;3 UBM/day</td>
<td>FDX 200 mg PO q12h (n=270) VAN 125 mg PO q6h (n=265)</td>
<td>Clinical cure,† mITT FDX (n=252): 87.7% (NI established vs. VAN) VAN (n=257): 86.8%</td>
</tr>
<tr>
<td>R, DB, MC, NI, phase III</td>
<td>Baseline characteristics: mean age, 63.4 years; infection with NAP1/B1/027 strain, 33.2%</td>
<td>Duration of treatment: 10 days Follow-up period: 28 days post-treatment</td>
<td>Clinical cure,† per-protocol population FDX (n=216): 91.7% VAN (n=235): 90.6%</td>
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<td>Recurrence rate,‡ mITT FDX (n=221): 12.7% (p=0.0002 vs. VAN) VAN (n=223): 26.9%</td>
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<td>Sustained response rate,§ mITT FDX (n=287): 74.6% (p=0.006 vs. VAN) VAN (n=307): 63.4%</td>
</tr>
<tr>
<td>Louie et al.</td>
<td>Patients (n=629) ≥16 years with acute, toxin-positive CDI and &gt;3 UBM/day</td>
<td>FDX 200 mg PO q12h (n=302) VAN 125 mg PO q6h (n=327)</td>
<td>Clinical cure,† mITT FDX (n=287): 88.2% (NI established vs. VAN) VAN (n=309): 85.8%</td>
</tr>
<tr>
<td>R, DB, MC, NI, phase III</td>
<td>Baseline characteristics: mean age, 61.6 years; infection with NAP1/B1/027 strain, 38.1%</td>
<td>Duration of treatment: 10 days Follow-up period: 28 days post-treatment</td>
<td>Clinical cure,† per-protocol population FDX (n=265): 92.1% VAN (n=283): 89.8%</td>
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<td>Recurrence rate,‡ mITT FDX (n=253): 15.4% (p=0.005 vs. VAN) VAN (n=265): 25.3%</td>
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<td>Sustained response rate,§ mITT FDX (n=287): 74.6% (p=0.006 vs. VAN) VAN (n=309): 64.1%</td>
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</table>

CDI = Clostridium difficile infection; DB = double-blind; FDX = fidaxomicin; MC = multicentre; mITT = modified intent-to-treat population; NI = non-inferiority; PO = orally; R = randomized; UBM = unformed bowel movements; VAN = vancomycin

* Subjects with life-threatening/fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon were excluded, as were patients with fulminant colitis and patients with multiple episodes of CDI (>1 prior episode in the previous 3 months).*
† The primary endpoint; clinical cure was defined by resolution of diarrhea (≤3 unformed bowel movements per day for 2 consecutive days), with maintenance of resolution for the duration of therapy and no further need for treatment (in the investigator's opinion) as of the second day after the last dose of study drug.
‡ Recurrence was defined as the return of >3 unformed bowel movements in a 24-hour period, a positive stool toxin test, and need for retreatment within 28–30 days of treatment completion.
§ Sustained response (also referred to as global cure) was defined as a clinical cure without recurrence.

WARNINGS, PRECAUTIONS & ADVERSE EFFECTS

The most notable warnings and precautions for fidaxomicin relate to a lack of data to support its use in certain patient populations, including:

- pediatric patients (<18 years of age);
- patients with pseudomembranous colitis, fulminant CDI, or life-threatening CDI;
- patients with inflammatory bowel disease (due to potential risk of enhanced absorption and systemic adverse events); and
- pregnant or nursing women.

The adverse effect profile of fidaxomicin is generally comparable to that of oral vancomycin. Based on a pooled analysis of data from the phase III studies, the product monograph reports that the most common adverse reactions (judged by clinical investigators as being possibly or definitely related to study medication administration)
in patients receiving fidaxomicin were nausea (2.7% vs. 3.4% with vancomycin), constipation (1.2% vs. 0.5%), and vomiting (1.2% vs. 1.4%). The overall frequency of treatment-emergent adverse events, and of mild, moderate, and severe adverse events, was similar in patients receiving fidaxomicin and vancomycin.9

A higher proportion of patients treated with fidaxomicin experienced neutropenia (2% vs. 1% with vancomycin) and gastrointestinal hemorrhage (4% vs. 2%); however, these events were not considered drug-related by the investigators.9

The product monograph should be consulted for a more detailed discussion of warnings, precautions, and adverse effects associated with fidaxomicin.

**DRUG INTERACTIONS**

The potential for clinically relevant drug interactions with fidaxomicin appears to be relatively low. Fidaxomicin and its major metabolite, OP-1118, have been reported to be weak inhibitors of cytochrome P-450 (CYP) enzymes,6 as well as substrates and inhibitors of the P-glycoprotein (P-gp) efflux transporter.5 Nonetheless, in vivo studies with prototypical medications, including warfarin, midazolam, omeprazole, cyclosporine, and digoxin resulted in no clinically significant pharmacokinetic alterations,7 and no dose adjustments have been recommended when fidaxomicin is used concurrently with medications that might alter CYP isoenzymes or the P-gp efflux transporter.4

Based on the high fecal concentrations achieved with fidaxomicin, there may be a potential for interactions with drugs that result in high levels of gastrointestinal binding, such as cholestyramine and sucralfate.11 In addition, minimum inhibitory concentration values for *C. difficile* for fidaxomicin have been reported to increase with increasing pH values *in vitro*; therefore, there is a theoretical interaction with drugs that can raise intestinal pH above 7.5 (e.g., proton pump inhibitors, histamine₂-antagonists).11 However, use of such medications was not listed as an exclusion criterion in the pivotal trials.12,13

**DOSAGE, ADMINISTRATION & MONITORING**

The recommended dose of fidaxomicin is 200 mg twice daily for 10 days, with or without food.4

No dosage adjustment is required for renal or hepatic impairment, and no specific laboratory monitoring is recommended by the manufacturer.9

**AVAILABILITY, STORAGE & COST**

Fidaxomicin is supplied as 200 mg film-coated tablets that come in bottles of 20.5 The product should be stored at temperatures between 15°C and 30°C.8

The price for a 20-tablet bottle from a national wholesaler is $2321.00. By comparison, the costs for a course of therapy with vancomycin (125 mg four times daily for 10 days) and generic metronidazole (500 mg three times daily for 10 days) are $360.08 and $21.08, respectively.

**DISCUSSION**

Recent guidelines for CDI recommend metronidazole as the initial treatment of choice for mild-to-moderate disease and vancomycin as the treatment of choice for severe disease.1,6,14,15 However, it has been reported that both of these agents are associated with relatively high rates of recurrent disease (20% to 30% of cases).16 Furthermore, efficacy of these drugs can decrease from 70% in the first recurrent episode of CDI to as low as 35% in additional recurrences.5

Fidaxomicin is comparable to vancomycin for initial clinical cure of mild to moderately severe CDI.12,15,17 Importantly, though, fidaxomicin is associated with lower recurrence rates than vancomycin, a finding considered to be highly clinically relevant.17 Notable attributes of fidaxomicin that may contribute to efficacy in sustaining clinical response and reducing recurrences are a low propensity to disrupt normal intestinal microflora16,18 and antispore effects.17,18 Furthermore, fidaxomicin seems unlikely to promote resistance to established antibiotic classes,17 and it was less likely than vancomycin to promote acquisition of VRE during CDI treatment.20

Further study is required to determine how fidaxomicin compares with metronidazole (particularly with respect to risk of recurrence), and to evaluate its efficacy in important patient subgroups excluded from the pivotal trials (e.g., those with pseudomembranous colitis, multiple recurrences of CDI, or inflammatory bowel disease).3,4,11,17 Data from larger groups of patients with severe/complicated CDI and patients infected with the NAP1/BI/027 strain of *C. difficile* would also be helpful, as would data regarding its use in refractory disease.3,4,21

Given that the price of fidaxomicin is significantly higher than that of currently recommended therapies for CDI, pharmacoeconomic analyses are warranted to evaluate the cost-effectiveness of this agent. If fidaxomicin is able to prevent costs associated with hospitalizations and complications resulting from recurrent CDI, then higher drug acquisition costs may be justified.

Firm recommendations regarding the place in therapy of fidaxomicin are hard to make based on available data, although suggested target populations for treatment have included patients with risk factors for recurrent CDI17 and patients with recurrent CDI who have not responded to treatment with the regimen used for the first episode of CDI.1

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1 Signs and symptoms of severe disease include fever (core body temperature >38.5°C), rigors, hemodynamic instability, peritonitis, ileus, toxic megacolon, pseudomembranous colitis, white blood cell count ≥15,000 cells/µL, and serum creatinine level ≥1.5 times the premorbid level.4,11,17

2 Hospitalizations and complications resulting from recurrent CDI, and the associated healthcare costs, have been estimated at $3,300,000,000 per year.6

3 Fidaxomicin was associated with lower recurrence rates than vancomycin and costs associated with the regimen were lower for fidaxomicin.
References


## NEW PRODUCTS/PRODUCT UPDATES

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<tr>
<td>Aloxi</td>
<td>Palonosetron</td>
<td>Eisai Limited</td>
<td>Anti-emetic (5-HT3 receptor antagonist)</td>
<td>0.5 mg capsules; packages of 1 0.25 mg/5 mL solution for injection (intravenous); packages of 1 x 5 mL single-use vial</td>
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<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>Eli Lilly Canada Inc.</td>
<td>Antihyperglycemic agent</td>
<td>New indication: For use in combination with insulin glargine (with or without metformin)</td>
</tr>
<tr>
<td>Caldolor</td>
<td>Ibuprofen</td>
<td>Alveda Pharmaceuticals Inc.</td>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>100 mg/mL solution for injection (intravenous); packages of 25 x 8 mL (800 mg) single-use vials</td>
</tr>
<tr>
<td>Cambia</td>
<td>Diclofenac potassium</td>
<td>Tribute Pharmaceuticals Canada Ltd.</td>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>Anticipated availability: October 2012 50 mg sachets of powder for oral solution; packages of 9</td>
</tr>
<tr>
<td>Caprelsa</td>
<td>Vandetanib</td>
<td>AstraZeneca Canada Inc.</td>
<td>Receptor tyrosine kinase inhibitor (for medullary thyroid cancer)</td>
<td>100 mg and 300 mg tablets; blister packages of 30</td>
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<tr>
<td>Cialis</td>
<td>Tadalafil</td>
<td>Eli Lilly Canada Inc.</td>
<td>cGMP-specific phosphodiesterase type 5 inhibitor</td>
<td>New indications: 1) Treatment of signs and symptoms of benign prostatic hyperplasia (BPH); 2) treatment of erectile dysfunction and signs of BPH</td>
</tr>
<tr>
<td>Cymbalta</td>
<td>Duloxetine hydrochloride</td>
<td>Eli Lilly Canada Inc.</td>
<td>Analgesic, antidepressant, anxiolytic</td>
<td>New indication: Management of chronic pain associated with osteoarthritis of the knee</td>
</tr>
<tr>
<td>Decapeptyl</td>
<td>Triptorelin acetate</td>
<td>Ferring Inc.</td>
<td>Luteinizing hormone-releasing hormone analog</td>
<td>0.1 mg/mL solution for injection (subcutaneous); packages of 7 x 1 mL and 28 x 1 mL pre-filled syringes</td>
</tr>
<tr>
<td>Dificid</td>
<td>Fidaxomicin</td>
<td>Optimer Pharmaceuticals Canada, Inc.</td>
<td>Antibacterial agent</td>
<td>200 mg tablets; bottles of 20</td>
</tr>
<tr>
<td>Durela</td>
<td>Tramadol hydrochloride</td>
<td>Cipher Pharmaceuticals Inc.</td>
<td>Opioid analgesic</td>
<td>100 mg, 200 mg, and 300 mg extended-release capsules; bottles of 7, 30, and 90</td>
</tr>
<tr>
<td>Emend IV</td>
<td>Fosaprepitant dimeglumine</td>
<td>Merck Canada Inc.</td>
<td>Neurikinin 1 (NK1) receptor antagonist</td>
<td>New indication: Prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy</td>
</tr>
<tr>
<td>Feraheme</td>
<td>Iron (as ferumoxytol)</td>
<td>Takeda Canada Inc.</td>
<td>Hematinic (for iron deficiency anemia)</td>
<td>30 mg/mL solution for injection (intravenous); packages of 10 x 17 mL single-use vials</td>
</tr>
<tr>
<td>Gliadel Wafer</td>
<td>Carmustine</td>
<td>Eisai Limited</td>
<td>Antineoplastic agent</td>
<td>Reinstatement of indication: As a treatment option in selected patients with newly-diagnosed high-grade malignant glioma for whom surgical resection is indicated, as an adjunct to surgery and radiation</td>
</tr>
<tr>
<td>Inlyta</td>
<td>Axitinib</td>
<td>Pfizer Canada Inc.</td>
<td>Kinase inhibitor, anti-tumour agent (for renal cell carcinoma)</td>
<td>1 mg and 5 mg tablets; bottles of 60 and blister packages of 28 and 56</td>
</tr>
<tr>
<td>Jakavi</td>
<td>Ruxolitinib</td>
<td>Novartis Pharmaceuticals Canada Inc.</td>
<td>Janus associated kinase 1,2 (JAK1,2) inhibitor (for myelofibrosis)</td>
<td>5 mg, 15 mg, and 20 mg tablets; bottles of 60 and blister packages of 56</td>
</tr>
<tr>
<td>Janumet</td>
<td>Sitagliptin/ metformin</td>
<td>Merck Canada Inc.</td>
<td>Oral antihyperglycemic agent, DPP-4 inhibitor, incretin enhancer</td>
<td>New indication: For use in combination with premixed or long/intermediate-acting insulin</td>
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</table>
| Januvia    | Sitagliptin  | Merck Canada Inc. | Oral antihyperglycemic agent, DPP-4 inhibitor, incretin enhancer | **New strengths:**
50 mg (for use in patients with moderate renal insufficiency) and 25 mg (for use in patients with severe renal insufficiency, including those with end-stage renal disease on dialysis)

**New indication:**
For use in combination with premixed or long/intermediate-acting insulin (with or without metformin)

| Olmetec   | Olmesartan medoxomil | Merck Canada Inc. | Angiotensin II AT₁ receptor blocker | **Extension of indication:**
Pediatric patients 6–16 years of age (for mild to moderate essential hypertension)

| Onglyza    | Saxagliptin | Bristol-Myers Squibb Canada | Oral antihyperglycemic agent, DPP-4 inhibitor, incretin enhancer | **New indication:**
For use in combination with premixed or long/intermediate-acting insulin (with or without metformin)

| Oralair | Grass pollen allergenic extract | Paladin Labs Inc. | Allergenic substance | 100 unit and 300 unit sublingual tablets; blister packages of 3 (100 unit), 28 (300 unit), and 30 (300 unit)

| Polymyxin B for Injection USP | Polymyxin B | SteriMax Inc. | Antibiotic | 50 mg powder for solution (intravenous, intramuscular, intrathecal, ophthalmic); packages of 1 vial

| Rasilez | Aliskiren | Novartis Pharmaceuticals Canada Inc. | Renin inhibitor | **Removal of indication:**
No longer indicated for concomitant use with angiotensin converting enzyme inhibitors and angiotensin receptor blockers

| Rebif | Interferon beta-1a | EMD Serono | Immunomodulator | **Extension of indication:**
Treatment of patients who have experienced a single demyelinating event, accompanied by an active inflammatory process and an abnormal MRI scan with lesions typical of MS, who are determined to be at high risk of developing clinically definite multiple sclerosis

| Revolade | Eltrombopag olamine | GlaxoSmithKline Inc. | Thrombopoietin receptor agonist | Change of dosing recommendations for patients having hepatic impairment with cirrhosis

| Tarceva | Erlotinib | Hoffmann-La Roche Ltd. | Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor | **New indication:**
As monotherapy for first-line treatment of patients with locally advanced (stage III b, not amenable to curative therapy) or metastatic (stage IV) non-small cell lung cancer with EGFR activating mutations

| Toviaz | Fesoterodine fumarate | Pfizer Canada Inc. | Anticholinergic, antispasmodic agent (for overactive bladder) | 4 mg and 8 mg extended-release tablets; bottles of 30 or blister packages of 28 and 84

| Votrient | Pazopanib | GlaxoSmithKline Inc. | Antineoplastic agent | **New indication:**
Advanced soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy

| Xalkori | Crizotinib | Pfizer Canada Inc. | Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (for ALK-positive non-small cell lung cancer) | 200 mg and 250 mg capsules; packages of 60

| Xeomin Cosmetic | *Clostridium botulinum* neurotoxin type A | Merz Pharma Canada Ltd. | Muscle relaxant, peripherally acting agent | 100 LD₅₀ units powder for solution (intramuscular); packages of 1, 2, 3, or 6 vials

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