



NEWS RELEASE

FDA Approves Merck's DIFICID® (fidaxomicin) to Treat *Clostridioides difficile* in Children Aged Six Months and Older

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KENILWORTH, N.J.--(**BUSINESS WIRE**)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the U.S. Food and Drug Administration (FDA) has approved a New Drug Application (NDA) for DIFICID® (fidaxomicin) for oral suspension, and a supplemental New Drug Application (sNDA) for DIFICID tablets for the treatment of *Clostridioides* (formerly *Clostridium*) *difficile*-associated diarrhea (CDAD) in children aged six months and older.¹

DIFICID is a macrolide antibacterial medicine indicated in adults and pediatric patients aged 6 months and older for treatment of CDAD. To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are proven or strongly suspected to be caused by *Clostridioides difficile* (*C. difficile*). DIFICID is contraindicated in patients who have known hypersensitivity to fidaxomicin or any other ingredient in DIFICID. DIFICID should only be used for the treatment of CDAD. DIFICID is not expected to be effective for treatment of other types of infections due to minimal systemic absorption of fidaxomicin.

"*C. difficile* is an important cause of health care- and community-associated diarrheal illness in children, and sustained cure is difficult to achieve in some patients. The fidaxomicin pediatric trial was the first randomized controlled trial of *C. difficile* infection treatment in children," said Dr. Larry K. Kociolek, Associate Medical Director of Infection Prevention and Control at Ann & Robert H. Lurie Children's Hospital of Chicago. "I am very excited to have a new *C. difficile* infection treatment option for my pediatric patients."

“Merck is committed to developing new treatments, as well as expanding indications of existing ones, in order to provide more solutions to treat infectious diseases, particularly among children,” said Dr. Nicholas Kartsonis, senior vice president, clinical research, infectious diseases and vaccines, Merck Research Laboratories. “C. difficile infection is an urgent public health challenge. We are grateful to the health care practitioners, the patients and their families for their invaluable contributions in helping to bring this new pediatric indication and the oral suspension formulation for DIFICID to the U.S. market.”

Both applications received a priority review classification by the FDA. The investigational pediatric indication for DIFICID was granted Orphan Drug Designation in 2010.

Data Supporting the Approval of DIFICID in Pediatric Patients

The FDA's approval of the new formulation and new indication for DIFICID was based on a Phase 3, multicenter, investigator-blind, randomized, parallel group study (known as the SUNSHINE study, NCT02218372), in which the safety and efficacy of fidaxomicin was evaluated in pediatric patients from 6 months to less than 18 years of age (one patient was less than six months of age). This study, sponsored by Astellas Pharma Europe B.V. (with Merck & Co., Inc. as collaborator) included 148 randomized patients aged <18 years with confirmed CDI, of whom 142 received either fidaxomicin (suspension or tablets, twice daily) or vancomycin (suspension or tablets, four times daily) in a 2:1 ratio. Patients were randomized by age group, as follows: 30 patients from 6 months to <2 years; 49 patients age 2 to <6 years, 40 patients age 6 to <12 years and 29 patients age 12 to <18 years. Generally, the two treatment groups were balanced regarding demographics and other baseline characteristics. CDAD clinical response in the overall pediatric population, assessed through two days following 10 days of treatment, was similar between the fidaxomicin and vancomycin groups (77.6% vs. 70.5% with a 95% CI for the treatment difference of 7.5 [-7.4%, 23.9%]). Sustained clinical response, defined as the proportion of treated patients with confirmed clinical response and no CDAD recurrence through 30 days after the end of treatment, was higher for fidaxomicin than for vancomycin (68.4% vs. 50.0% with a 95% CI for the treatment difference of 18.4 [1.5%, 35.3%]).

The safety of DIFICID in pediatric patients 6 months to less than 18 years of age was evaluated in a Phase 2 single-arm trial in 38 patients and a Phase 3 randomized, active-controlled trial in 98 patients treated with DIFICID and 44 patients treated with vancomycin. Treatment discontinuation due to adverse reactions occurred in 7.9% (3/38) of patients in the Phase 2 trial, and in 1% (1/98) and 2.3% (1/44) of DIFICID- and vancomycin-treated patients, respectively, in the Phase 3 trial. The most common selected adverse reactions occurring in ≥5% of pediatric patients treated with DIFICID in the Phase 3 trial were pyrexia (13.3%), abdominal pain (8.2%), vomiting (7.1%), diarrhea (7.1%), constipation (5.1%), increased aminotransferases (5.1%) and rash (5.1%). One death occurred in the Phase 2 single-arm trial and three deaths occurred in the Phase 3 trial of DIFICID-treated patients. No deaths occurred in vancomycin-treated patients during the study period (40 days). All deaths occurred in patients less than

2 years of age and appeared to be related to underlying comorbidities.

About *Clostridioides difficile*

Clostridioides (formerly *Clostridium*) *difficile*, also known as *C. difficile* or *C. diff*, is one of the most common causes of health care-associated infections in U.S. hospitals.² Recent estimates suggest *C. difficile* causes almost 500,000 infections annually in the United States and is associated with approximately 29,000 deaths within 30 days of initial diagnosis.³ According to the CDC's Antibiotic Resistance Threats in the United States, 2019 (2019 AR Threats Report), *C. difficile* is categorized as an urgent threat and is stated as a public health threat that requires urgent and aggressive action.⁴

Important Safety Information about DIFICID (fidaxomicin)

DIFICID is contraindicated in patients who have known hypersensitivity to fidaxomicin or any other ingredient in DIFICID.

Acute hypersensitivity reactions, including dyspnea, rash, pruritus, and angioedema of the mouth, throat and face have been reported with DIFICID. If a severe hypersensitivity reaction occurs, DIFICID should be discontinued and appropriate therapy should be instituted.

DIFICID is not expected to be effective for the treatment of other types of infections due to minimal systematic absorption of fidaxomicin. DIFICID has not been studied for the treatment of infections other than CDAD. DIFICID should only be used for the treatment of CDAD.

Only use DIFICID for infection proven or strongly suspected to be caused by *C. difficile*. Prescribing DIFICID in the absence of a proven or strongly suspected *C. difficile* infection is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

The most common adverse reactions reported in adults are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%) and neutropenia (2%).

The most common adverse reactions in pediatric patients are pyrexia (13.3%), abdominal pain (8.2%), vomiting (7.1%), diarrhea (7.1%), constipation (5.1%), increased aminotransferases (5.1%) and rash (5.1%).

Among patients receiving DIFICID (fidaxomicin), 33 (5.9%) withdrew from trials as a result of adverse reactions. Vomiting was the primary adverse reaction leading to discontinuation of dosing (incidence of 0.5% for both DIFICID and vancomycin patients).

The safety and effectiveness of DIFICID have not been established in pediatric patients younger than 6 months of age.

The recommended dose for adults is one 200 mg DIFICID tablet orally twice daily for 10 days, with or without food.

The recommended dose for pediatric patients weighing at least 12.5 kg and able to swallow tablets is one 200 mg DIFICID tablet administered orally twice daily for 10 days. If unable to swallow tablets, pediatric patients may be dosed with DIFICID oral suspension based on weight. DIFICID oral suspension should be administered orally twice daily for 10 days.

No dose adjustment is recommended for patients 65 years of age or older.

No dose adjustment is recommended for patients with renal impairment.

No dosage adjustments are recommended when co-administering DIFICID with substrates of P-gp or CYP enzymes.

The impact of hepatic impairment on the pharmacokinetics of DIFICID has not been evaluated; however, because DIFICID and its active metabolite (OP-1118) do not appear to undergo significant hepatic metabolism, elimination of DIFICID and OP-1118 is not expected to be significantly affected by hepatic impairment.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to

significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2018 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see U.S. Prescribing Information for DIFICID (fidaxomicin) at https://www.merck.com/product/usa/pi_circulars/d/dificid/dificid_pi.pdf, and Patient Information for DIFICID (fidaxomicin) at https://www.merck.com/product/usa/pi_circulars/d/dificid/dificid_ppi.pdf.

1 DIFICID in the US and Canada is a trademark of Cubist Pharmaceuticals LLC, an indirect wholly-owned subsidiary of Merck Sharp & Dohme Corp.

2 Lessa, Fernanda. "Burden of Clostridium difficile Infection in the United States." *The New England Journal of Medicine*, vol. 372, Feb. 2015, pp.825-834.

3 Ibid.

4 "Antibiotic Resistance Threats in the United States, 2019." U.S. Centers for Disease Control and Prevention, 2019, p. 65.

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