Pharmacotherapeutic report (summary)
Fidaxomycin (Dificlir®) for the indication *'Clostridium difficile-related disease'*

Recommendation by CVZ dated 25 February 2013, based on Evaluation by the WAR (Scientific Advisory Committee)

Medicine. Fidaxomycin (Dificlir®), film-coated tablets 200 mg

Registered indication. "Use on adults for the treatment of *Clostridium difficile-related infections",* also referred to as "*C. difficile*-associated diarrhoea"

Posology. 200 mg 2 twice daily during 10 days.

Mechanism of action. Fidaxomycin is a narrow-spectrum antibiotic with a bactericidal effect on *C. difficile*. The drug inhibits bacterial RNA-polymerase and thus RNA-synthesis. The specificity of the effect is partly because fidaxomycin inhibits the RNA-polymerase of *C. difficile* at a 20X lower concentration than that necessary to inhibit the *E. coli* enzyme. There is in vitro evidence that fidaxomycin inhibits the spore-forming of *C. difficile.*

Summary of the therapeutic value

Intended effects. Fidaxomycin was not compared with the first-choice drug metronidazole, but with the second-choice drug, vancomycin, in patients with a first-time *Clostridium difficile*-related disease (CDAD) or a first-time CDAD-recurrence. In 2 studies fidaxomycin was not inferior to vancomycin in bringing the diarrhoea to an end. However, fidaxomycin resulted in fewer recurrences in the month after treatment than when vancomycin was used. In the Netherlands the only indication for treating CDAD with antibiotics is when a patient is severely ill or has been admitted to hospital. The post-hoc analyses in these sub-groups suggest similar results to those of the total study group. There are no known data on the efficacy of fidaxomycin in patients with a $\geq 2^{nd}$ CDAD-recurrence, nor in patients with extremely severe CDAD. A systematic review has revealed that vancomycin is just as effective as metronidazole in treating patients with CDAD.

Unintended effects. Fidaxomycin and vancomycin seem to have equivalent side effects profiles. Metronidazole has the most favourable side effect profile. To date, fidaxomycin has no resistance problem, metronidazole hardly any, while vancomycin sometimes does.

Experience. Experience with fidaxomycin is limited while considerable experience has been obtained with metronidazole and vancomycin.

Applicability. Globally, the applicability of fidaxomycin is just as broad as that of metronidazole and vancomycin. Fidaxomycin's registered indication does not include children.

Ease of use. Fidaxomycin is easier to use than metronidazole and vancomycin which require more frequent doses. There is no evidence that this leads to a difference in efficacy.

Final conclusion.

Considerations. The published studies in which fidaxomycin was compared with vancomycin had the following limitations: (a) patients who were severely ill or had a $\geq 2^{nd}$ recurrence were

excluded from the studies; (b) the studies include all sorts of patients with CDAD; the data relevant to the Dutch situation were obtained from post-hoc sub-group analyses; (c) the follow-up lasted only 1 month. Based on the studies, fidaxomycin is just as effective as vancomycin. Fidaxomycin was not compared with metronidazole, though metronidazole is known to be just as effective as vancomycin in cases of CDAD. Due to the limitations mentioned, there are insufficient useful data to be able to speak of an added value of fidaxomycin above vancomycin or above metronidazole in the treatment of patients with CDAD.
Final conclusion. In the treatment of patients with CDAD who are severely ill or who have been admitted to hospital, the therapeutic value of fidaxomycin is comparable with that of metronidazole and vancomycin.

*The original text of this **WAR-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's WAR-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.