Cost-effectiveness of Fidaxomicin (Dificlir®) tablets for the treatment of adults with *Clostridium difficile*-associated diarrhoea.

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1. Fidaxomicin is indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD). Fidaxomicin is the first in a new class of macrocylic antibiotics. The main therapeutic advantage of fidaxomicin over current treatment options is the capacity to decrease the risk of recurrence in patients with CDI.

2. Astellas submitted an economic evaluation for the use of fidaxomicin for the treatment of CDI compared with oral metronidazole (used to treat initial non-severe CDI and first non-severe recurrence) and oral vancomycin (used to treat severe CDI and any non-severe recurrence beyond the first one). A target population of all CDI patients was chosen for the base case. Three additional patient subgroups were considered: patients with non-severe CDI; patients with severe CDI and patients with a first CDI recurrence. The evaluation was conducted from the HSE perspective.

3. Two clinical studies were presented as direct evidence of the benefit of fidaxomicin compared with vancomycin. Both studies shared an almost identical study design and had essentially similar results (Louie *et al.* and Cornely *et al.*). The primary endpoint of the trials was clinical cure and the secondary endpoints included recurrence rate and a composite endpoint of sustained cure. Treatment differences according to various subgroups (including disease severity and previous C. difficile infection) were assessed in post-hoc analysis. In both studies, fidaxomicin was found to be non-inferior to vancomycin in terms of clinical cure. Fidaxomicin demonstrated significantly lower recurrence rates and significantly higher sustained cure rate than vancomycin. The review group note that there is limited experience of using fidaxomicin in seriously ill patients and in patients with severe comorbidities. Furthermore, there is currently no evidence for the use of fidaxomicin beyond the first recurrence of CDI.

4. The review group note that many of the patients included in the trials had mild to moderate disease (approximately 60%). For these patients clinical guidelines recommend initial treatment with metronidazole. No clinical trials

have directly compared metronidazole and fidaxomicin. The manufacturer submitted an indirect treatment comparison between fidaxomicin and metronidazole in patients with non-severe CDI. This was based on a single centre randomised controlled trial comparing metronidazole and vancomycin (Zar et al. n=150) and the fidaxomicin studies.The review group consider that the results of the indirect comparison should be interpreted with caution as there was considerable heterogeneity between the study by Zar et al. and the fidaxomicin studies. There were differences in baseline characteristics, sample sizes, clinical settings and study time frames.

5. The manufacturer developed a Markov model to demonstrate the cost-effectiveness of fidaxomicin. The time horizon was one-year as it was considered unlikely that patients would experience recurrence beyond this period. For the base case analysis it was assumed that 25% of prescribing would be on the High Tech Drug scheme and the remainder in the hospital setting. The treatment pathways in the model were based on interviews with Irish clinical microbiologists and appear to reflect clinical practice. Resource utilisation data were derived from literature and expert opinion. It was assumed that 98% of infected patients in the hospital setting would be treated in an isolation room.

6. Health related quality of life (HRQoL) data was not included as an outcome measure in the pivotal clinical trials. Consequently, utilities were derived from the literature. HRQoL associated with CDI was based on the utility associated with being hospitalised. There is considerable uncertainty associated with the utility estimates. However, the review group note that this parameter was varied appropriately in sensitivity analysis.

7. Fidaxomicin was less costly and more effective than current standard of care. The based case analysis estimated that fidaxomicin compared to current standard of care in all patients wtih CDI would result in cost savings of €2,904 and incremental QALYs of 0.031, giving an ICER of €-94,128/QALY. The main drivers of cost-effectiveness were the reduction in rate of recurrence in patients treated with fidaxomicin and the cost of hospitalisation. The cost-

effectiveness of fidaxomicin was also investigated separately for patients with non-severe CDI (€-92,403/QALY), severe CDI (€-128,335/QALY) and patients with a first CDI recurrence (€-144,834/QALY). Fidaxomicin was found to be dominant (more effective and less costly) in the base case and for all patient subgroups.

8. One-way and probabilistic sensitivity analysis were conducted. The ICERs were highly sensitive to recurrence rates. The ICER fell to €-231,717/QALY when the odds ratio of experiencing a recurrence in patients with a history of two or more previous recurrences was set to the upper 95% confidence interval. The ICER increased to €688,953/QALY when the odds ratio experiencing a recurrence with fidaxomicin in patients with a first recurrence was set to the upper 95% confidence interval. ICERs were also sensitive to the cost of hospitalisation. However, when the cost of hospitalisation was decreased by 20% in the model, fidaxomicin was still dominant for all patient sub-groups. The probabilistic sensitivity analysis demonstrates that there is an 82% probability that fidaxomicin is cost-effective in all CDI patients at a willingness to pay threshold of €45,000/QALY.

9. The budget impact analysis was performed over a five year time horizon and assuming that 25% of fidaxomicin prescribing would be on the High Tech Drug Scheme and the remainder in the hospital setting. The gross drug budget impact was estimated to range from approximately €88,000 in year one to approximately €1.55 million by year five. The net budget impact was estimated to increase from €20,000 in year one to €0.3 million by year five. This includes the cost offsets from replacing prescriptions for vancomycin and metronidazole and reduced hospitalisation from recurrences avoided. The review group have concerns that the reduction in hospital costs due to reduced length of stay from reduced recurrence rates may be overestimated as many of these patients will have co-morbidities which may prolong hospital stay.

10. Fidaxomicin was found to be dominant (more effective and less costly) in the base case analysis for all patients with CDI and for all patient subgroups.

Fidaxomicin is significantly more expensive than metronidazole and vancomycin. The estimates of cost-effectiveness are driven mainly by the relative reductions in recurrence of CDI which are subject to significant uncertainty. However, evaluation of the combined uncertainty in probabilistic sensitivity analysis demonstrates that there is an 82% probability that fidaxomicin is cost-effective in all CDI patients at a willingness to pay threshold of €45,000/QALY. Fidaxomicin should only be prescribed according to the recommendations outlined in the recently updated National Clostridium *difficile* guidelines (due to be completed in February 2013 www.hpsc.ie).

References:

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3. Zar F, Bakkanagari S, Moorthi K et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-Associated Diarrhoea, stratified by disease severity. Clin Infect Dis 2007; 45: 302-307