Reply to Hardalo et al., “Myelosuppression with Oxazolidinones: Are There Differences?”

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In our study evaluating thrombocytopenia adverse event reports with linezolid and tedizolid using the FDA Adverse Event Reporting System (FAERS), we addressed the well-known limitations of FAERS, including unknown incidence, rare events with wide confidence intervals, overreporting/underreporting (Weber effect), misclassification, differing postapproval periods, and missing information (1). These limitations of FAERS have been well described in the literature for approximately 15 years (2–5) and are clearly disclosed on the FAERS website (6).

Hardalo et al. resummaries these recognized FAERS limitations; however, there are three points that require further clarification. First, adverse event surveillance systems and studies of adverse event reports can detect safety signals and, indeed, have correctly identified new adverse effects, as well as new information about known adverse effects resulting in labeling changes and market withdrawal (5, 7–9). The signals indicate a finding that needs further investigation, meaning signals are hypothesis generating and neither imply nor confirm causal associations. It should be noted that we did not “draw conclusions about the comparative safety profiles between tedizolid and linezolid” in our article. We agree that several clinical trials and a single FAERS study cannot sufficiently describe the real-world safety profile of a newer medication. In reality, even with many years of drug utilization and numerous studies of varied designs and in diverse populations, the actual safety profiles of some medications may still not be fully understood (a few examples of this include rosiglitazone, statins, and fluoroquinolones) (10–13).

Second, Hardalo et al. state that comparative safety profiles can only be determined from randomized, controlled clinical trials. However, clinical trials are not considered good indicators of postmarketing safety because of their well-known limitations, including small sample sizes, healthy-diseased populations, subjective and/or proxy endpoints, and subjective and potentially unblinded adverse event adjudication, as well as restrictive protocols that do not reflect eventual real-world utilization (7–9, 14, 15). As we mentioned in our article, the risk of thrombocytopenia observed with linezolid postapproval was substantially higher than that observed in clinical trials (16–18). Accurate real-world safety profiles develop from cumulative knowledge of agreement between studies of different designs and in different populations, as we know from both theory and experience (5, 7–9, 19).

Lastly, all studies have strengths and limitations; therefore, cumulative knowledge of safety also depends on the quality and reporting of each individual study. While some limitations are well known and understood, such as the limitations of FAERS, others are less known and may be difficult to discern if not explicitly disclosed. For example, the limitations of pooling clinical trial data were not discussed in the pooled analysis of ESTABLISH-1 (20) and ESTABLISH-2 (21), which reported a “lower incidence of thrombocytopenia... among patients who received tedizolid” (22). The benefits of random-

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ization may not apply to pooled data; therefore, pooled data can be subject to the same limitations as observational studies, including confounding by known and unknown factors (23–26). Furthermore, the findings from pooled analyses may contradict the findings from individual studies (Simpson's paradox) (26). Therefore, the preferred approaches for combining data include meta-analytic methods or traditional analytic methods to control confounding (23–26).

As with any new medication, cumulative knowledge from all studies, including clinical trials, prospective and retrospective observational studies, meta-analyses, adverse event reporting, and case series, will be integral to understanding the real-world safety profile of tedizolid.

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