Sodium Oxybate Post-Marketing Surveillance

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As a condition of approval, the Food and Drug Administration required the manufacturer of Xyrem (sodium oxybate; Jazz Pharmaceuticals, Inc., Palo Alto, CA) to establish and maintain a risk management program. Required elements of this program include the use of a single central pharmacy to ship sodium oxybate directly to patients and gather adverse event (AE) data including deaths which are reported to the FDA. The results of a post-marketing safety study¹ indicated 30 fatalities had occurred in patients prescribed sodium oxybate from 2002 through early 2008, although most were determined to be unrelated to the medication.

In a report filed with the U.S. Securities and Exchange Commission,² Jazz Pharmaceuticals recently revealed the central pharmacy failed to report the deaths of 74 additional patients who received sodium oxybate between 2003 and 2010 and were not reported to the FDA. In most instances, the cause of these deaths was not specified. Jazz indicated in their report that the adjusted annual all-cause mortality rate did not constitute a new safety signal; nevertheless, it is concerning that Jazz Pharmaceuticals did not communicate this information directly to sodium oxybate prescribers. While it remains to be seen whether these 74 deaths are related to the use of the drug, they serve as a reminder to prescribers that sodium oxybate should be used with caution in patients with obesity or other known risk factors for sleep-disordered breathing.³

It is also troubling that the actual number of deaths is unknown because a well-recognized flaw of passive reporting systems is their reliance on physicians to voluntarily report serious AEs, including fatalities. Studies indicate underreporting of AEs by physicians ranges from 86-96%,^{4,5} including serious and fatal events. Reasons include the belief that serious AEs are already well known, it is not possible to determine the relatedness of an AE to the drug, an AE report will not contribute to medical knowledge, or only unique AEs must be reported.⁶

The spontaneous reporting of adverse drug reactions is the primary means for supporting the FDA post-marketing safety surveillance program, physicians are encouraged to report known and suspected adverse drug reactions to manufacturers and the Food

and Drug Administration. MedWatch Form 3500 for voluntary reporting of AEs including instructions and a postage-paid, pre-addressed mailer is available online: <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>.

Based on the failure noted above, 3rd party surveillance by a non-stakeholder should become the standard and be the rule for mandated risk management programs. Jazz Pharmaceuticals should conduct a prospective study using active surveillance rather than passive physician reporting.

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