FDA's New Risk Evaluation and Mitigation Strategy for Opioids

According to a recent report by the Substance Abuse and Mental Health Services Administration, prescription drug abuse continues to be a grave problem in the United States (US)[1]. A prominent shift in the misuse of prescription opiates between 1999 and 2009 (which increased steadily from 1% of admissions for those aged 12 and older in 1999 to 7% in 2009, and increased from 8% to 33% of all opiate admissions) was reported. Alternately, during the same time period hospital admissions related to methamphetamine/amphetamines rose from 4% to 6%, marijuana admissions increased from 13% to 18%, and cocaine-related admissions decreased from 14% to 9%[1]. These figures highlight the relative rise in prescription drug misuse compared to illicit drugs. Of interest in relation to last issue's CNS Watch on suicidality, another report suggested suicide attempts involving narcotic pain relievers increased by 79.5% for males of 35 to 49 years of age, and by 193.3% for those 50 years and older from 2005 to 2009 [2]. Clearly, prescription abuse is a major issue for clinicians and CNS drug developers, and this data lends credence to some of the long-held perceptions of misuse and diversion that are barriers to ensuring proper pain treatment.

The US Food and Drug Administration (FDA) had also recognised a substantial increase in the number of post-marketing reports of abuse, misuse, addiction and overdose in this time period resulting in fatalities associated with extended-release and/or long-acting opioid drugs. It was this trend that led to the deliberation of various risk mitigation strategies over the past several years, as evidenced by various public and private meetings with a variety of pain and healthcare specialists, patients, and pharmaceutical industry members. These meetings eventually culminated in the FDA's announcement this April that all long-acting and extended-release opioid medications will be required to have a Risk Evaluation and Mitigation Strategy (REMS).

The opioid REMS mandate was carried out under section 505-1 of the Federal Food, Drug, and Cosmetic Act, and as a crucial element of a multi-agency plan to reduce prescription drug abuse. The FDA Amendments Act (FDAAA) of 2007 grants the FDA the authority to require a REMS from manufacturers "…to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse". Thus, in "the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class"[3].

Although many companies and organisations have endorsed the employment of a class-wide REMS programme, others have suggested that the FDA has failed to meet the scientific burden to impose a REMS programme on a class-wide basis. They suggest instead that REMS must be product-specific according to the FDAAA; and that class-wide REMS are by nature cumbersome, impractical and most importantly lack the flexibility to effectively address issues unique to specific medications[4]. It should be noted that individual REMS for several analgesic drug products have already been in use, including generic morphine sulfate alone, which has a Medication Guide, and morphine sulfate and naltrexone hydrochloride (HCL) extended-release capsules (EMBEDATM) which has a Medication Guide and Communication Plan as part of the REMS. Furthermore, the notion of class-wide REMS has already been advanced and is well accepted (e.g., erythropoiesis-stimulating agents) in other therapeutic areas.

Nonetheless, the current class-wide REMS constitutes the most far-reaching REMS to date with implications for practitioners, hospital staff, pharmacists, patients and analgesia drug developers. Specifically, the current REMS mandate affects multiple CNS drug developers and numerous drugs including, but not limited to, hydromorphone HCL extended-release capsules, methadone HCL tablets, morphine sulfate extended-, controlled- and sustained-release capsules, morphine sulfate and naltrexone extended-release capsules, oxycodone HCL controlled-release tablets, oxymorphone HCL extended-release tablets, hydromorphone HCL extended-release tablets, and Fentanyl Transdermal System, Buprenorphine Transdermal System, as well as innumerable generic drug products.

The scope of this class-wide REMS programme was outlined in a letter to sponsor companies from Bob A. Rappaport, M.D., the Director of the Division of Anesthesia and Analgesia Products at the FDA. This letter delineated the key elements of the REMS including both a Medication Guide and elements to assure safe use ("ETASU"), as well as a timetable for submission of assessments[3]. In this letter the FDA noted that a Medication Guide was necessary for patients' safe and effective use of drug, and that this Medication Guide should have both common content applicable to all extended-release and long-acting opioids, as well as product specific information necessary for safe and effective use of the drug.

Under 21 CFR 208, sponsor companies are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed drug products. The REMS must also minimally ensure that training is provided to prescribers who prescribe these drugs. To aid this, a summary of the content of such a training programme was provided, including information on patient selection and assessment, considerations when prescribing opioids, managing patients taking opioids, initiating and modifying doses of opioids for chronic pain, maintenance over time, as well as product specific information and

patent counselling[3]. The FDA expects that the training will be conducted by an accredited, independent continuing medical education (CME) provider. In terms of duration, the FDA expects the training to take at least a couple of hours; however, the length of time will depend on how the CME and CE providers develop the programme. It is also possible to link the training required under the REMS to general training in pain management[5].

The FDA anticipates that appropriate sponsor companies will provide unrestricted grants to CME/CE providers to help pay for the development and execution of these educational programmes, and that cost-sharing amongst sponsor companies would occur. An independent audit of the quality of the content of educational materials used by CME providers is also required as part of the REMS assessment plan, with audit frequency to be specified. This audit would need to be performed by a third party with the goal of keeping the educational material free of any promotional content[5]. Also required is an assessment of how many prescribers of long-acting and extended-release opioids have successfully completed the training, with performance goals related to how many prescribers are expected to be trained within certain periods of time (e.g., 50% of prescribers trained within six months; 70% within 12 months).

The assessment plan should also include the following elements along with the methodology for each element: an evaluation of patients' understanding of the serious risks of these drug products; an evaluation of drug utilisation patterns; an evaluation of changes in prescribing behavior; a surveillance plan that includes monitoring for misuse, abuse, overdose, addiction, and death as well as any intervention to be taken resulting from signals of these metrics. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with these products must also be included. Last of all, the REMS must also incorporate a proposed timetable for submission of assessments that should be no less frequent than six months, 12 months, and annually, after the REMS is initially approved. The letter ends by stating that within 120 days of the date of this letter, the sponsor must submit the proposed REMS as a supplement to their NDA. These REMS will need to be updated periodically as new products are approved[3].

It is acknowledged that it may take several months to develop these REMS. In the meantime, healthcare professionals should continue to prescribe long-acting and extended-release opioids, and are encouraged to thoroughly discuss the risks and benefits of these products with their patients. Patients who are currently taking long-acting or extended-release opioids should continue to take their medications as directed, and any patients who have concerns about their medications should consult with their healthcare professional. The FDA fully appreciates that the institution of a class-wide programme such as this might make it more cumbersome for patients to receive the proper pain treatment that they need. Therefore, as part of the REMS, the FDA will monitor patient access to medicines and continue to dialogue with patients and physicians to ensure that patients are treated properly. Finally, it should be noted that the FDA is open to additional discussions with industry before August 17, the REMS due date. For questions and further information please refer to the FDA's website on Opioid Drugs and Risk Evaluation and Mitigation Strategies[6], or contact them directly at OpioidREMS@fda.hhs.gov.

References:

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