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ISMP Calls for Immediate Communication between Industry and FDA on Opioid Product Withdrawals

Horsham, Pa.—A recent warning letter from the Food and Drug Administration (FDA) directing companies to stop making and distributing unapproved dosage forms of specific narcotics may have unintended safety consequences. The Institute for Safe Medication Practices (ISMP) is calling for the FDA to work more closely with pharmaceutical manufacturers to address potential safety issues that may arise from the required opioid product withdrawals, especially the removal of morphine concentrate oral liquid from the marketplace.

Since morphine concentrate oral liquid (ROXANOL and generics) is one of the 14 unapproved concentrations listed by the FDA in its April 1, 2009 communication, it would not be available unless a new drug application is submitted and approved. The FDA noted that there are approved products containing the same active ingredients as those on the list, including different opioids that can be used to relieve pain. They have determined that stopping production of the unapproved products will not create a shortage for consumers. However, it could create serious patient treatment problems. For example:

- **More Difficult Pain Control for Patients Needing End of Life Care**. Many cancer patients, especially those near end of life with decreased level of consciousness but who can still be treated adequately with large doses of oral morphine to control pain, will have much more difficulty swallowing 10 mg/5 mL or 20 mg/5 mL morphine liquid than the 20 mg/mL liquid currently available.

- **Possible Increase in Alternative Methods to Obtain Morphine Concentrate Solution**. Pharmacies may be asked to prepare morphine concentrate solutions and may not have the quality control mechanisms of large scale manufacturers to avoid the risk of calculation, preparation, packaging, labeling, and dropper calibration errors. Not all pharmacies may be able to meet these safety expectations and the needs of patients requiring these solutions.

- **Possible Increase in Administration Errors**. Some patients will have to be switched to injectable morphine or another route such as suppository, which are less comfortable and more difficult to administer. Others will be switched to another opioid on an equianalgesic basis, such as fentanyl buccal or patches or methadone, thus risking the possibility of miscalculation errors when converting or temporary intolerance or periods of inadequate analgesia.

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It is clear that many opioid products could benefit from a safety review process. Confusion between products has in the past sometimes lead to dosing errors and fatalities have been reported. Morphine oral concentrate solution could be reviewed to better assure that the dosing device, formulation, and labeling maximally protect against user error.

As one example, companies have labeled morphine solutions prominently as 20 mg/mL or 20 mg/5 mL, sometimes leading to confusion between the two (see *ISMP Medication Safety Alert!* newsletter, Oral morphine alert, October 30, 2003 issue). Accidental selection of the wrong concentration, and prescribing/labeling the product by volume, not milligrams, contributes to these errors. A required approval process could lead to labeling of the concentrate as 100 mg/5 mL to help clarify the high concentration and distinguish it from 20 mg/5 mL. The concentrate is currently packaged without a prominent warning that it is highly concentrated.

The withdrawal notice requiring manufacturers to submit a new drug application for review in order to continue producing unapproved concentrations of morphine occurred in the midst of FDA's implementation of required opioid risk evaluation and mitigation strategies (REMS) for manufacturers. Coordination of these efforts could have made it less difficult for the healthcare community to accommodate and respond to the changes in availability.

ISMP hopes that FDA and the pharmaceutical industry will be able to work together to ensure that a safe version of morphine oral concentrate liquid will be available.

For more information, see the latest issue of the *ISMP Medication Safety Alert!* newsletter at: www.ismp.org/Newsletters/acutecare/articles/200904091.asp

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