Information for Healthcare Professionals

Methadone Hydrochloride

The issues described in this communication have been addressed in product labeling.

FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias

FDA has reviewed reports of death and life-threatening adverse events such as respiratory depression and cardiac arrhythmias in patients receiving methadone. These adverse events are the possible result of unintentional methadone overdoses, drug interactions, and methadone's cardiac toxicities (QT prolongation and Torsades de Pointes). Physicians prescribing methadone should be familiar with methadone's toxicities and unique pharmacologic properties. Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid-tolerant. Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients how to take methadone. Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report serious adverse events associated with the use of these drugs, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations

Methadone is an effective analgesic and may provide pain relief when other analgesics are ineffective. However, methadone can cause significant toxicities. We are highlighting important safety information from the new label about using methadone for pain. See the methadone label (Dolophine) for more details.

Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects. During treatment initiation, methadone's full analgesic effect is usually not attained until 3-5 days of dosing. Initiation and titration to analgesic effect and dose adjustments should be done cautiously and in consideration of these properties. In chronic use, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations.

Cross-tolerance between methadone and other opioids is incomplete. This incomplete cross-tolerance makes the conversion of patients on other opioids to methadone complex and does not eliminate the possibility of methadone overdose, even in patients tolerant to other opioids. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists to methadone. It is critical to understand the pharmacokinetics of

methadone when converting patients from other opioids to methadone. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose adjustments.

Methadone can cause serious cardiac conduction effects, including QT interval prolongation and Torsades de Pointes.

There are pharmacokinetic and pharmacodynamic drug interactions between methadone and many other drugs. Drugs administered concomitantly with methadone should be evaluated for interaction potential.

Methadone is secreted into human milk.

What should physicians do?

- Read and follow the prescribing information for methadone.
- Carefully weigh methadone's risks with its potential benefits before prescribing methadone.
- Avoid prescribing methadone 40 mg dispersible tablets for pain. This product is only FDA-approved for detoxification and maintenance treatment of narcotic addition.
- Closely monitor patients who receive methadone, especially during treatment initiation and dose adjustments.

What should healthcare professionals tell patients when prescribing methadone for pain?

- Pain relief from methadone does not last as long as methadone stays in your body. Therefore, do not to take more methadone than prescribed because methadone could build up in your body and cause death.
- Methadone can cause life-threatening changes in breathing (it may slow or stop).
- Methadone can cause life-threatening changes to the heart beat that may not be felt.
- Seek medical attention right away if you experience symptoms suggestive of an arrhythmia such as palpitations, dizziness, lightheadedness, or fainting or if you experience symptoms suggestive of a methadone overdose such as slow or shallow breathing; extreme tiredness or sleepiness; blurred vision; inability to think, talk or walk normally; and feeling faint, dizzy or confused.
- Directions you should follow if your pain is not controlled after taking the prescribed amount of methadone.
- Pain relief from methadone should last longer after you have taken it for awhile.

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- Tell your doctor if you start or stop other medicines because other medicines can interact with methadone and possibly cause death or life threatening side effects, or result in less pain relief from methadone.
- Tell your doctor if you are breastfeeding because methadone is secreted into human milk. Babies can experience the same serious side effects from methadone as the mother.

Data and Background Information

There have been reports of serious adverse events such as death, respiratory depression, and serious cardiac arrhythmias in patients receiving methadone. Fatalities have been reported in patients who were switched from chronic, high-dose treatment with other opioids to methadone and in patients initiating treatment with methadone. These adverse events may have resulted from unintentional methadone overdoses, drug interactions, and/or methadone's cardiac toxicities (QT prolongation and Torsades de Pointes). Some of the unintentional overdoses were due to prescribers not being aware of methadone's pharmacokinetics and potential adverse effects.

FDA recently updated the methadone label following an extensive review of the medical literature and other available information. The new label provides new information on methadone's pharmacology, drug interactions, and instructions on converting patients from other opioids to methadone and dosing methadone based on a synthesis of recommendations from several palliative care organizations and treatment centers.

References

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- Pain Management at the End of Life. A Physician's Self-Study Packet. For physicians with prescribing privileges. A Collaborative Project of the Main Hospice Council, Maine Pain Initiative, University of Southern Maine, Muskie School of Public Service, 2006. http://www.mainehospicecouncil.org/Pain%20Management%20web%20version.pdf (accessed 10/20/06)
- Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage*. 2001 Aug;22(2): 672-87.