

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Tramadol Hydrochloride XL

Product:

TRAMADOL HYDROCHLORIDE XL
(Zytram XL®)
150mg, 200mg, 300mg, and 400mg
controlled release tablets

Class of drugs: Synthetic narcotic
analgesic (pain reliever)

Indication:

Management of moderate pain

Manufacturer: Purdue Pharma Inc.

CED Recommendation-

The CED recommended that tramadol hydrochloride XL (Zytram XL) not be listed on the Ontario Drug Benefit (ODB) Formulary, on the basis that there is insufficient evidence demonstrating a therapeutic advantage over currently funded pain relievers.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer did not approve funding of tramadol hydrochloride XL (Zytram XL).

Status

No funding through the Ontario Public Drug Programs.

Highlights of Recommendation:

- ◆ A review of the evidence submitted by the manufacturer showed no advantage to using tramadol hydrochloride XL over other pain relievers already listed on the Ontario Drug Benefit Formulary.
- ◆ There were no published studies comparing tramadol hydrochloride XL with other long-acting narcotic pain relievers.
- ◆ The clinical studies were of short duration while patients with chronic pain may take pain relievers indefinitely. The CED was concerned about the lack of evidence and safety data for the long-term use of tramadol hydrochloride XL.
- ◆ At the submitted price, tramadol hydrochloride XL costs less than some long-acting narcotic pain relievers such as oxycodone and fentanyl used for severe pain. However, it is more expensive than other narcotic pain relievers (such as codeine / acetaminophen, oxycodone / acetaminophen), long-acting formulations of morphine and many non-narcotic pain relievers.
- ◆ **Overall, the CED noted that the current evidence does not support a therapeutic or safety advantage for tramadol hydrochloride XL over currently funded pain relievers.**

Background:

Tramadol hydrochloride is a synthetic narcotic pain reliever. Tramadol hydrochloride XL is a long-acting product for the management of moderate pain in adults who require continuous pain relievers for several days or longer.

Detailed Discussion:

- ◆ In this review, the CED considered one proprietary, unpublished study. The manufacturer does not permit the Ministry to share the details of this proprietary information. However, the CED noted there was no difference in pain relief between tramadol hydrochloride XL and the comparator used.
- ◆ The CED noted that tramadol hydrochloride XL is a long-acting narcotic pain reliever. The trial provided by the manufacturer did not compare tramadol hydrochloride XL to another long-acting narcotic pain reliever which would be the most clinically relevant comparator. There was no evidence that tramadol hydrochloride XL offers a therapeutic advantage over any formulary alternatives, including narcotic or non-narcotic pain relievers.
- ◆ Tramadol hydrochloride XL is indicated for patients who require treatment for several days or more, but there was no data in the manufacturer's submission supporting its long-term use.
- ◆ Tramadol hydrochloride XL is partially a pro-drug which means it requires metabolism in the liver by the enzyme cytochrome P450 (CYP) 2D6 to its active form to provide pain relief. Approximately 7% of the population does not have the enzyme and cannot convert tramadol hydrochloride XL to its active form, leading to lack of benefit. Another 10% of patients have excessive enzyme levels and convert more of the drug to the active form, which can lead to higher incidences of side effects. The CED had concerns with the efficacy of tramadol hydrochloride in under-metabolizers due to less active drug being available in the body and the safety in over-metabolizers due to more active drug being available in the body.
- ◆ The CED expressed significant concerns with the safety of the extended release formulation if crushed or chewed. There were also concerns with the

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potential for abuse and dependence, a significant issue with other weaker narcotic pain relievers. The submitted study did not assess the potential development of drug tolerance and the need for higher doses with long-term use, withdrawal reactions and dependency.

- ◆ In addition, the CED expressed concerns over the risk of diversion of tramadol hydrochloride, as seen with other narcotic pain relievers, such as oxycodone.
- ◆ Tramadol hydrochloride XL costs less than some of the long-acting narcotics such as oxycodone and fentanyl used for severe pain. However, it is more expensive than other pain relievers (such as codeine/acetaminophen, oxycodone/acetaminophen) and other long-acting formulations of morphine and non-narcotic pain relievers.
- ◆ **Overall, the CED noted that the clinical evidence provided by the manufacturer did not support a therapeutic or safety advantage for tramadol hydrochloride XL over currently funded narcotic and non-narcotic pain relievers.**

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that tramadol hydrochloride (Zytram XL) controlled release tablets not be listed.



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