

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Tramadol Hydrochloride ER

Product:

TRAMADOL HYDROCHLORIDE ER
(Tridural®)
100mg, 200mg, and 300mg extended-
release tablets

Class of drugs: Synthetic narcotic
analgesic (pain reliever)

Indication:

Management of moderate pain

Manufacturer: Paladin Labs

CED Recommendation-

The CED recommended that tramadol hydrochloride ER (Tridural) 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 ER (Tridural).

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 ER over other pain relievers already listed on the Ontario Drug Benefit Formulary.
- ◆ There were no published trials comparing tramadol hydrochloride ER with other long-acting narcotic pain relievers.
- ◆ Published systematic reviews found that tramadol hydrochloride was more effective compared to placebo for chronic pain conditions. However, these reviews did not assess extended-release formulations separately.
- ◆ At the submitted price, tramadol hydrochloride ER 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 ER over currently available narcotic and non-narcotic pain relievers.**

Background:

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

Detailed Discussion:

- ◆ The manufacturer provided three trials of 12-week duration that evaluated the efficacy and safety of tramadol hydrochloride ER.
 - ◇ Study MDT3-002 (Mongin et al. *Clin Drug Invest* 2004; 545-558) is a randomized, double-blind trial comparing tramadol hydrochloride ER once daily with short-acting tramadol twice daily in patients with pain due to osteoarthritis;
 - ◇ Study MDT3-003 (Fishman et al. *J Opioid Manag* 2006; 3(5): 273-80) is a randomized, placebo-controlled trial to assess safety and efficacy of tramadol hydrochloride ER at 100mg, 200mg and 300mg doses for patients with pain due to osteoarthritis;
 - ◇ Study MDT3-005 (Burch et al. *J Pain Symptom Manage* 2007; 34 (3): 328-38) is a randomized, double-blind, placebo-controlled, trial assessing the efficacy, safety and clinical benefit for patients with pain due to osteoarthritis.
- ◆ Study MDT3-002 demonstrated confirmed that tramadol hydrochloride taken once daily is not inferior to short acting tramadol hydrochloride taken twice daily in providing pain relief.
- ◆ The two placebo-controlled trials demonstrated statistically significant pain relief for tramadol hydrochloride ER compared to placebo and that there was a dose-effect relationship for pain relief.
- ◆ The CED noted that tramadol hydrochloride ER is a long-acting narcotic pain reliever. The manufacturer did not provide any trials comparing tramadol hydrochloride ER to other long-acting narcotic pain relievers, which would be the most clinically relevant comparators, or to other non-narcotic pain relievers. There was no evidence that tramadol hydrochloride ER offers a therapeutic advantage over any formulary alternatives, including narcotic or non-narcotic pain relievers.

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- ♦ Tramadol hydrochloride 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 to its active form, leading to lack of benefit. Another 10% of patients have excessive enzyme and converts more of the drug to the active form which can lead to higher incidences of side effects. The CED has concerns with the efficacy of tramadol hydrochloride ER 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 safety of the extended release formulation if crushed or chewed. There were also concerns with the potential for abuse and dependence, a significant issue with other narcotic pain relievers.
- ♦ In addition, the CED expressed concerns over the risk of diversion of tramadol hydrochloride ER as seen with other narcotics such as oxycodone.
- ♦ Tramadol hydrochloride ER 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 narcotic 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 ER 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 (Tridural) extended-release tablets not be listed.



Ministry of
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