

## Recommendations and Reasons

Committee to Evaluate Drugs (CED)

# Tramadol Hydrochloride ER

### Product:

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

**Class of drugs:** Synthetic narcotic  
analgesic (pain reliever)

### Indication:

Management of moderate pain

### Manufacturer:

Biovail Pharmaceuticals Canada

## CED Recommendation-

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

## 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 two multi-centre, randomized, double-blind, placebo-controlled trials, of 12-weeks duration, evaluating the safety and efficacy of tramadol hydrochloride ER for patients with osteoarthritis (Babul et al. *J Pain Symptom Manage* 2004 and Gana et al. *Curr Med Res Opin* 2006). Both trials demonstrated improvement in pain intensity over baseline for tramadol hydrochloride ER compared to placebo. The incidence of adverse events was significantly higher for patients treated with tramadol hydrochloride ER compared to placebo.
- ◆ An open-label, one-year, uncontrolled study (Pascual et al. *Curr Med Res Opin* 2007), also provided by the manufacturer, evaluated the safety and efficacy of tramadol hydrochloride ER for patients with chronic non-cancer pain. This study showed that pain relief was sustained over the course of the study and that patients did not develop tolerance (the loss of effect over time requiring higher doses to maintain the same effect).
- ◆ The CED also considered a double-blinded, randomized-controlled trial (Delemos et al. *Am J Ther* 2010 Mar 3) comparing tramadol hydrochloride ER once daily (100mg, 200mg or 30mg daily), celecoxib 200mg daily and placebo over 12 weeks in patients with osteoarthritis. Only tramadol hydrochloride ER 300mg demonstrated significant difference from placebo on the patients' global assessment of disease activity.
- ◆ The CED noted that tramadol hydrochloride ER is a long-acting narcotic analgesic. The only comparator trial did not compare tramadol hydrochloride ER to another long-acting narcotic pain reliever which would be the most clinically relevant comparator. 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 the 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 (Ralivia) extended-release tablets not be listed.



Ministry of  
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