# CLINICAL UPDATE

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| **Brand Name** | Qdolo® |
| **Generic Name** | tramadol hydrochloride |
| **Drug Manufacturer** | Athena Bioscience, LLC |

## Clinical Update

### TYPE OF CLINICAL UPDATE

Clinical Update - New formulation (5 mg/mL oral solution)

### FDA APPROVAL DATE

September 1, 2020

### LAUNCH DATE

September 11, 2020

### REVIEW DESIGNATION

Standard

### TYPE OF REVIEW

Type 3 - New Dosage Form

### DISPENSING RESTRICTIONS

N/A

## Overview

### INDICATION(S) FOR USE

It is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Qdolo® for use in patients for whom alternative treatment options (e.g., non-opioid analgesics):

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

### MECHANISMS OF ACTION

It contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is

only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

## DOSAGE FORM(S) AND STRENGTH(S)

Oral Solution: tramadol hydrochloride 5 mg/mL

## DOSE & ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.
- Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy and following dosage increases with Qdolo® and adjust the dosage accordingly.
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with Qdolo®. Consider prescribing naloxone based on the patient's risk factors for overdose.
- Start at 25 mg /day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg /day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg /day (50 mg four times a day). After titration, Qdolo® 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg /day.
- Severe hepatic impairment: Recommended dose is 50 mg every 12 hours.
- Do not abruptly discontinue Qdolo® in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide.

## EFFICACY

Tramadol hydrochloride has been given in single oral doses of 50, 75, and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg tramadol hydrochloride tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

Tramadol hydrochloride has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol hydrochloride. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of tramadol hydrochloride in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX) daily.

Titration Trials

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily tramadol hydrochloride dose of 200 mg (50 mg four times per day), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate tramadol hydrochloride therapy using slower titration rates. A 16-day titration schedule, starting with 25 mg every morning and using additional doses in 25 mg increments every third day to

100 mg / day (25 mg four times per day), followed by 50 mg increments in the total daily dose every third day to 200 mg / day (50 mg four times per day), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule (See Figure 2).

**Figure 2:**