



## Tramadol Dosage Forms

The analgesic activity of tramadol is due to both the parent drug tramadol, and the O-demethylated M1 metabolite. Tramadol is metabolized hepatically by CYP2D6 to the more pharmacologically active M1 metabolite.

At least two complementary processes appear responsible for the mechanism of action:

- binding of the parent moiety (low affinity) and the M1 metabolite (higher affinity than parent tramadol but less than other opioids) to  $\mu$ -opioid receptors, causing inhibition of ascending pain pathways in the central nervous system
- weak inhibition of reuptake of norepinephrine and serotonin

Tramadol is indicated for moderate to moderately severe pain in adults. Long-acting dosage forms are indicated for adults who require continuous treatment for several days or more.<sup>1</sup>

Due to differences in pharmacokinetic properties, the various tramadol dosage forms are not considered interchangeable.<sup>2</sup>

Single ingredient tramadol dosage forms currently (2017) available in Canada<sup>1</sup>:

### **Immediate Release (IR)**

Ultram, Apo-Tramadol

### **Extended Release (XL, ER)**

Durela

Ralivia

Tridural, Taro-Tramadol ER

Zytram XL

Table 1 compares the characteristics of these products. Most information is provided by the manufacturers, which explains the differences in dose titrations, maximum daily recommended doses, administration recommendations, etc.

**Table 1: Comparison of Tramadol Dosage Forms<sup>3-9</sup>**

Name of Product	Dosage Form	Available Strengths	Pharmacokinetics	Drug-Food Interaction	Additional Comments
Ultram, Apo-Tramadol	IR Tablet	50mg	<ul style="list-style-type: none"> <li>- Onset: within 1h</li> <li>- Peak effect: 2-3h</li> <li>- Half-life: tramadol ~6-7h M1 ~ 7-9h</li> <li>- C<sub>ss</sub>: within 2 days with QID dosing</li> </ul>	<ul style="list-style-type: none"> <li>- Administered without regard to food</li> <li>- Rate and extent of absorption not significantly affected by food</li> </ul>	<ul style="list-style-type: none"> <li>- Maximum daily dose not to exceed 400mg</li> <li>- For chronic pain, start at 25mg daily and titrate up with divided doses every 3 days to 50mg - 100mg QID</li> </ul>
Durela	ER Capsules –contains an IR tablet and ER beads	100mg (25mg IR + 75mg ER) 200mg (50mg IR + 150mg ER) 300mg (50mg IR + 250mgER)	<ul style="list-style-type: none"> <li>- Onset: within 1h followed by a consistent release over ~ 24h</li> <li>- C<sub>ss</sub>: 5 days with once daily dosing</li> </ul>	<ul style="list-style-type: none"> <li>- Administered without regard to food</li> <li>- Rate and extent of absorption not significantly affected by food</li> <li>- Capsules to be swallowed whole</li> </ul>	<ul style="list-style-type: none"> <li>- Maximum daily dose 300mg</li> <li>- Once daily dosing starting with 100mg and titrating with ≥ 5 days between dose adjustments</li> </ul>
Ralivia	ER Tablets –polymer diffusion-based film and semi-permeable coating	100mg, 200mg, 300mg	<ul style="list-style-type: none"> <li>- Lag-time to onset with peak plasma levels at 12-15h</li> <li>- C<sub>ss</sub>: 4 days with once daily dosing.</li> </ul>	<ul style="list-style-type: none"> <li>- T<sub>max</sub> delayed by ~3 h when administered with food</li> <li>- Can be administered without regard to food as long as administration is consistent</li> <li>- Tablets should be swallowed whole</li> </ul>	<ul style="list-style-type: none"> <li>- Maximum daily dose 300mg</li> <li>- Once daily dosing starting with 100mg and titrating with ≥ 5 days between dose adjustments</li> </ul>
Tridural	ER Tablets <b>Tridural</b> –outer IR matrix and an inner ER core	100mg, 200mg, 300mg (25% IR, 75% ER)	<ul style="list-style-type: none"> <li>- Onset: within 1h followed by SR phase providing a smooth plasma concentration/ time profile.</li> <li>- C<sub>ss</sub>: 48h with once daily dosing.</li> </ul>	<ul style="list-style-type: none"> <li>- Rate and extent of absorption not significantly affected by food</li> <li>- Consistent once daily dosing at breakfast is recommended</li> </ul>	<ul style="list-style-type: none"> <li>- Maximum daily dose 300mg</li> <li>- Once daily dosing starting with 100mg and titrating in 100mg increments every 2 days</li> <li>- For maximum dose of 300mg/day, titration should take at least 4 days</li> </ul>

<b>Taro-Tramadol ER</b>	<b>Taro-Tramadol ER</b> -based on osmotic drug delivery - ingredients contained within a non-absorbable shell which slowly releases drug at a constant rate over time			<b>Taro brand</b> - Non-absorbable shell is passed into the stool after the drug is absorbed	- Although description of these tablet formulations differs, the pharmacokinetics are the same -Interchangeable by some insurance plans <sup>10,11</sup>
<b>Zytram XL</b>	CR Tablets - matrix tablet	75mg, 100mg, 150mg, 200mg, 300mg, 400mg	- Tmax ~6 hours. - Css: 3 to 4 days with once daily dosing - At Css, 150mg daily = 50mg IR q8h	- Administered without regard to food - Empty matrix tablet remnants may be visible in the stool, or via colostomy	- Maximum daily dose 400mg - Treatment generally initiated at 150mg with slow titration of dosage adjustments separated by 7 days
<b>CR = controlled release; Css = steady state; ER= extended release; h=hour(s); IR = immediate release; SR = sustained release</b>					

**References:** 1. CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2017 [cited 2017 Sep 20]. Available from: <http://www.e-therapeutics.ca>. Also available in paper copy from the publisher. 2. Kizilbash A, Ngô-Minh C. Review of extended-release formulations of Tramadol for the management of chronic non-cancer pain: focus on marketed formulations. *J Pain Res* 2014;7:149-61. 3. Product monograph for Apo-Tramadol 50mg. Apotex Inc. Toronto, ON M9L 1T9. 11 Jun 2014. 4. Product monograph for Durela. Cipher Pharmaceuticals Inc. Mississauga, ON L5N 8K4. 20 Dec 2016. 5. Product monograph for Ralivia. Valeant Canada LP. Laval, QC H7L 4A8. 21 Dec 2016. 6. Product monograph for Taro-Tramadol ER. Taro Pharmaceuticals Inc. Brampton, ON L6T 1C1. 5, Sep 2017. 7. Product monograph for Tridural. Paladin Labs Inc. Saint-Laurent, QC H4M 2P2. 20 Dec 2016. 8. Product monograph for Ultram. Janssen Inc. Toronto ON M3C 1L9. 04 Jan 2017. 9. Product monograph for Zytram XL. Purdue Pharma. Pickering, ON L1W 3W8. 15 May 2017. 10. Green Shield Canada. Enhanced generic substitution drug list. 2011; cited 18 Sep 2017. Available from: [https://www.providerconnect.ca/Carriers/GreenShield/Pharmacy/PharmacyManuals/en\\_CA/EGSDrugListAPR27\\_2011.pdf](https://www.providerconnect.ca/Carriers/GreenShield/Pharmacy/PharmacyManuals/en_CA/EGSDrugListAPR27_2011.pdf) 11. Ontario Drug Benefit Formulary. Interchangeable grouping. [updated 04 Oct 2016; cited 18 Sep 2017]. Available from: <https://www.formulary.health.gov.on.ca/formulary/interchangeable.xhtml?drugId=02450445>