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 µ-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.¹

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

Single ingredient tramadol dosage forms currently (2017) available in Canada¹:
- 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>
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<tr>
<th>Name of Product</th>
<th>Dosage Form</th>
<th>Available Strengths</th>
<th>Pharmacokinetics</th>
<th>Drug-Food Interaction</th>
<th>Additional Comments</th>
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</table>
| Ultram, Apo-Tramadol | IR Tablet | 50mg | - Onset: within 1h  
- Peak effect: 2-3h  
- Half-life: tramadol ~6-7h  
M1 ~ 7-9h  
- Css: within 2 days with QID dosing | - Administered without regard to food  
- Rate and extent of absorption not significantly affected by food | - Maximum daily dose not to exceed 400mg  
- For chronic pain, start at 25mg daily and titrate up with divided doses every 3 days to 50mg - 100mg QID |
| Durela | ER Capsules  
-contains an IR tablet and ER beads | 100mg (25mg IR + 75mg ER)  
200mg (50mg IR + 150mg ER)  
300mg (50mg IR + 250mgER) | - Onset: within 1h followed by a consistent release over ~ 24h  
- Css: 5 days with once daily dosing | - Administered without regard to food  
- Rate and extent of absorption not significantly affected by food  
- Capsules to be swallowed whole | - Maximum daily dose 300mg  
- Once daily dosing starting with 100mg and titrating with ≥ 5 days between dose adjustments |
| Ralivia | ER Tablets  
-polymer diffusion-based film and semi-permeable coating | 100mg, 200mg, 300mg | - Lag-time to onset with peak plasma levels at 12-15h  
- Css: 4 days with once daily dosing. | - Tmax delayed by ~3 h when administered with food  
- Can be administered without regard to food as long as administration is consistent  
- Tablets should be swallowed whole | - Maximum daily dose 300mg  
- Once daily dosing starting with 100mg and titrating with ≥ 5 days between dose adjustments |
| Tridural | ER Tablets  
Tridural  
-outer IR matrix and an inner ER core | 100mg, 200mg, 300mg (25% IR, 75% ER) | - Onset: within 1h followed by SR phase providing a smooth plasma concentration/time profile.  
- Css: 48h with once daily dosing. | - Rate and extent of absorption not significantly affected by food  
- Consistent once daily dosing at breakfast is recommended | - Maximum daily dose 300mg  
- Once daily dosing starting with 100mg and titrating in 100mg increments every 2 days  
- For maximum dose of 300mg/day, titration should take at least 4 days |
| Taro-Tramadol ER | 75mg, 100mg, 150mg, 200mg, 300mg, 400mg | - T_max ~6 hours. 
- C:S: 3 to 4 days with once daily dosing 
- At C:S, 150mg daily = 50mg IR q8h | - Administered without regard to food 
- Empty matrix tablet remnants may be visible in the stool, or via colostomy |
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<tr>
<td>Zytram XL CR Tablets</td>
<td>75mg, 100mg, 150mg, 200mg, 300mg, 400mg</td>
<td>- Maximum daily dose 400mg</td>
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<td>CR Tablets - matrix tablet</td>
<td>- Treatment generally initiated at 150mg with slow titration of dosage adjustments separated by 7 days</td>
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</table>

CR = controlled release; C:S = steady state; ER= extended release; h=hour(s); IR = immediate release; SR = sustained release

**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.