

## Amantadine Hydrochloride Shortage

### Suppliers of amantadine in Canada.<sup>1</sup>

DIN	Strength/ Dosage Form	Manufacturer
01990403	100 mg capsule	PMS
02022826	10 mg/ml syrup	PMS

### Shortage Management

- According to McKesson (Pharmaclik)<sup>2</sup>:
  - 50mg/5ml syrup as of March 7, 2017, no date available.
  - 100mg capsules should be available by March 20, 2017.
- Bulk powder is available for extemporaneous compounding (e.g. through Medisca<sup>3</sup>)

### Indications for amantadine<sup>4</sup>:

- prevention and treatment of Influenza A infections; it has no appreciable activity against Influenza B virus
- treatment of early stage Parkinson's disease (PD) as monotherapy
- treatment of drug-induced extrapyramidal symptoms, including levodopa-induced dyskinesia

### Therapeutic alternatives for:

#### A. Influenza Prevention

- Immunization with trivalent inactivated influenza vaccine remains the primary tool for the prevention of influenza infection and illness.<sup>5</sup>
- Chemoprophylaxis with the antiviral agents oseltamivir (Tamiflu) and zanamivir (Relenza) is most useful for the long-term care environment when given as soon as possible to all residents who are not yet ill, regardless of their vaccination status, as well as to non-immunized care providers.<sup>5</sup>
- Regarding oseltamivir during community outbreaks, duration of protection lasts for the length of dosing period; safety and efficacy have been demonstrated for use up to 6 weeks in immunocompetent patients and safety has been demonstrated for use up to 12 weeks in patients who are immunocompromised.<sup>6</sup>
- Amantadine has exhibited high levels of resistance and is therefore no longer recommended for prophylaxis.<sup>5</sup>
- See Table 1 for doses.

#### B. Influenza Treatment<sup>5</sup>

- For maximum benefit, treatment must begin within two days after the onset of symptoms.

- The use of antiviral agents for treatment of influenza in healthy children and adults is not recommended.
- Antivirals can be considered for treatment in individuals 1–64 years of age who have a chronic condition or who are immunocompromised and in those ≥65 years when influenza is either strongly suspected or confirmed.
- Early treatment with **oseltamivir** may reduce influenza-related complications in children ≤2 years of age, as well as adults and children >2 years at high-risk of complications.
- See Table 1 for doses.

Table 1: Antiviral Doses for Prophylaxis and Treatment of Influenza <sup>6-8</sup>				
Antiviral	Patient	Dose	Prophylaxis	Treatment
<b>Oseltamivir</b>	≤15 kg	30 mg	ONCE daily within 2 days of exposure to symptomatic index case. Continue for ≥10 days; if index case is child or elderly, continue up to 14 days. <sup>†</sup>	TWICE daily within 2 days of symptom onset. Continue for 5 days.
	>15 kg to 23 kg	45 mg		
	>23 kg to 40 kg	60 mg		
	> 40 kg	75 mg		
<b>Zanamivir*</b>	<i>Household</i> (7 years and older)	10 mg	ONCE daily within 36 hours of exposure to symptomatic index case. Continue for 10 days	TWICE daily within 2 days of symptom onset. Continue for 5 days.
	<i>Community</i> (e.g. long term care) (13 years and older)	10 mg	ONCE daily within 5 days of outbreak. Continue for 28 days.	

<sup>†</sup>Viral shedding may continue up to 14 days in children and the elderly.<sup>6</sup>

\*Relenza inhaler device may be difficult to use for some patients.<sup>5</sup> Zanamivir is not recommended for those with severe underlying respiratory disease.<sup>8</sup>

### C. Parkinson's Disease<sup>9-11</sup>

1. **Levodopa** is the most effective drug for the symptomatic treatment of Parkinson's Disease (PD) and is the drug of first choice if symptoms, particularly those related to bradykinesia, become intrusive or troublesome.<sup>9</sup>
  - **Carbidopa-levodopa (Sinemet)**
    - **Dosing**<sup>12</sup> -Treatment should begin with small doses, such as 25/100 mg, one-half tablet two to three times daily with meals. Once initiated without side effects, the total daily dose of carbidopa-levodopa can be titrated carefully upward over several weeks to a full tablet of 25/100 mg three times daily as tolerated. Older adults or those with dementia should begin with smaller doses and slower titration because of their increased susceptibility to psychiatric side effects.
  - **Benserazide-levodopa (Prolopa)**
    - **Dosing**<sup>13</sup> - The initial recommended dose is one capsule of Prolopa 100/25 mg once or twice a day. This dose may be carefully increased by one capsule every third or fourth day until an optimal therapeutic effect is obtained without dyskinesias. Near the upper limits of dosage, the increments should be made slowly, at two to four week intervals

for example. The dosage should be divided, aiming at a frequency of dosing of at least four times daily taken with or immediately after meals.

2. **Selective monoamine oxidase (MAO) type B inhibitors** - Uncertainty remains about the relative risks and benefits of MAO B inhibitors, as few trials compared them with other antiparkinson medications.
  - **Selegiline** is modestly effective as symptomatic treatment for PD and may have neuroprotective properties. The use of selegiline in early PD is a reasonable option as long as the patient understands its limitations.
    - **Dosing**<sup>14</sup> -2.5mg to 5mg daily, administered with breakfast and lunch to minimize interference with sleep.
    - Maximum dose – 5mg twice daily.
  - **Rasagiline** has neuroprotective properties in animal models and appears modestly effective as symptomatic treatment for PD in human clinical trials.
    - **Dosing**<sup>15</sup> - For monotherapy and adjunctive therapy to dopamine agonists, the recommended dose for the treatment of PD is 1 mg once daily.
    - For adjunct therapy to levodopa therapy, the dose is 0.5-1 mg once daily. The recommended initial dose is 0.5 mg administered once daily. If response is not achieved, it may be increased to 1 mg once daily.
    - The maximum dose in both monotherapy and adjunct therapy is 1 mg once daily.
3. **Centrally acting anticholinergic drugs** such as trihexyphenidyl and benzotropine have been used for many years in PD and continue to have a useful role.
  - **Trihexyphenidyl** is the most widely prescribed anticholinergic agent, although there is little evidence to suggest that one drug in this class is superior to another.
    - **Dosing**<sup>16</sup> — PD: Initial dose 1 mg daily. Increase by 2 mg daily at intervals of 3–5 days, up to 6–10 mg daily in 3 divided doses with food. Usual maintenance dose is 2 mg TID.
  - **Benzotropine** traditionally is more commonly used by psychiatrists for the management of antipsychotic drug-induced movement disorders.
    - **Dosing**<sup>17</sup> - PD: Initial dose: 0.5–1 mg daily. Usual dose: 1–2 mg twice daily. Some will experience optimal relief taking the entire daily dose at bedtime; others respond more favorably to divided doses.
    - Maximum dose: 6 mg per day. A maximum dose of 4 mg/day has been recommended for elderly patients.
4. **Dopamine Agonists** - are not as effective as levodopa and not as well tolerated in elderly patients.<sup>11</sup>
  - **Bromocriptine**
    - **Dosing**<sup>18</sup> –1.25 mg twice daily, increased by 2.5 mg daily in 2- to 4-week intervals as needed. Usual maximum dose 30mg/day.
  - **Pramipexole**
    - **Dosing**<sup>19</sup> –start at 0.125 mg three times daily and gradually increase at intervals no more frequent than every 5 to 7 days. Pramipexole was effective and well-tolerated over a dosage range of 1.5 to 4.5 mg/day, administered in equally divided doses three times per day, as monotherapy or in combination with levodopa (approximately 800

mg/day). When used in combination, a reduction of the levodopa dosage should be considered.

- **Ropinirole**
  - **Dosing<sup>20</sup>** -The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as directed by product monograph. Initial benefits were observed with 3 mg/day and higher. Doses greater than 24 mg/day have not been evaluated in clinical trials.
- **Rotigotine** (transdermal patch)
  - **Dosing<sup>21</sup> - Early-stage Parkinson's disease:** A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.
  - **Dosing<sup>21</sup> - Advanced-stage Parkinson's disease:** A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.
  - Each patch is to be replaced every 24 hours.
  - Application sites include abdomen, shoulder, upper arm, thigh, hip, or flank, and should be rotated.

#### **D. Drug-induced Extrapyrarnidal Symptoms**

- Anticholinergics such as bantzropine should not be used beyond the period necessary to counteract the extrapyramidal manifestations (parkinsonian symptoms, acute dystonic reaction). Evaluate the need for continued therapy regularly.
- Anticholinergic agents should be used to treat parkinsonian symptoms on a short-term basis, not as prophylaxis. Evaluate the need for continued treatment regularly.
- **Bantzropine<sup>17</sup>**
  - Parkinsonian symptoms: 1–4 mg once or twice daily orally or parenterally.
  - Acute dystonic reactions: 2 mg IM or IV, then 1–2 mg twice daily for 2–3 days
- **Trihexyphenidyl<sup>16</sup>**
  - Initial dose: 1 mg per day. If necessary, subsequent doses may be increased until satisfactory symptomatic control is achieved (usual range 5–15 mg per day in 3–4 divided doses).

Prepared by Jean Macpherson BSP; reviewed by Karen Jensen MSc, BSP and Carmen Bell BSP  
medSask, March 2017

## References:

1. Health Canada. Drug Product Database Online Query. Ottawa, ON: Health Canada; [accessed 06 Mar 2017]. Available from: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp> .
2. McKesson Canada c2017 Pharmaclik; [accessed 07 Mar 2017]. Available from: <https://clients.mckesson.ca/catalog>. Account required.
3. Amantadine in: Chemicals search page. Medisca. [accessed 06 Mar 2017]. Available from: <https://www.medisca.ca/products/compounding-chemicals> Account required.
4. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Amantadine; [updated 01 Oct 2009; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
5. RxTx[Internet]. Ottawa (ON): Canadian Pharmacists Association; 2016. Bowles S, Strang R. Influenza; [updated 01 Nov 2015; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca>
6. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Tamiflu; [updated 26 Jan 2015; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
7. Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2017 [cited 03 Mar 2017]. Available from: <http://online.lexi.com> Subscription required.
8. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Relenza; [updated 29 May 2012; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
9. Tarsy, D. Pharmacologic treatment of Parkinson disease. In: UpToDate, Basow, DS (Ed), Waltham MA, 2017. Cited 30 Jul 2015. Available from [www.uptodate.com](http://www.uptodate.com). Subscription and login required
10. Grimes D, Grodon J, Snelgrove, B, et al. Canadian guidelines on Parkinson's disease introduction. Can J Neurol Sci. 2012; 39: Suppl 4: S1-S30.
11. PL Detail-Document, Parkinson's Disease Therapy Algorithm. Pharmacist's Letter/Prescriber's Letter. July 2015.
12. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Sinemet; [updated 06 Feb 2014; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
13. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Prolopa; [updated 15 Mar 2016; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
14. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Selegiline CPhA monograph; [updated 01 Nov 2011; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
15. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Azilect; [updated 20 Nov 2014; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
16. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Trihexyphenidyl CPhA monograph; [updated 01 Nov 2011; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
17. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Benzotropine CPhA monograph; [updated 01 Nov 2011; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
18. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Bromocriptine CPhA monograph; [updated 01 Oct 2013; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
19. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Mirapex; [updated 27 Nov 2012; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
20. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: ReQuip; [updated 22 Jul 2015; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>
21. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. CPS online: Neupro; [updated 09 Sep 2014; cited 11 Feb 2017]. Available from: <https://www.e-therapeutics.ca/>