Ropinirole 0.25 mg Shortage

Table 1: Canadian Suppliers of Ropinirole[1]

Product	Strength	DIN	Manufacturer
ACT Ropinirole	0.25 mg	02316846	Teva Canada Limited
	1 mg	02316854	
	2 mg	02316862	
	5 mg	02316870	
JAMP-Ropinirole	0.25 mg	02352338	JAMP Pharma Corporation
	1 mg	02352346	
	2 mg	02352354	
PMS-Ropinirole	0.25 mg	02326590	Pharmascience Inc
	1 mg	02326612	
	2 mg	02326620	
Ran-Ropinirole	0.25 mg	02314037	Ranbaxy Pharmaceuticals Canada Inc
	1 mg	02314053	
	2 mg	02314061	
	5 mg	02314088	
Ropinirole	0.25 mg	02353040	Sanis Health Inc
	1 mg	02353059	

Health Canada Approved Indications of Ropinirole[2]:

- treatment of signs and symptoms of idiopathic Parkinson disease (PD)

Off-Label Uses of Ropinirole[3]:

- treatment of moderate to severe primary restless legs syndrome (RLS) (FDA-approved)

Background

Ropinirole 0.25 mg tablets are currently unavailable; while higher strengths may be available (e.g. 1 mg, 2 mg, 5 mg), the shape of the tablets makes them unsuitable for splitting.

Management Options

Pharmaceutical Alternatives

- 0.25 mg capsules can be compounded using existing commercial product, while available.

Therapeutic Alternatives

- The closest alternative to ropinirole is pramipexole, which is also used for PD and RLS.
    - ropinirole's dosing range (0.25 mg to 24 mg daily) is much wider than pramipexole's (0.125 mg to 4.5 mg daily), making dose conversions at the upper end difficult
    - so long as higher ropinirole strengths are available, only patients on low doses need to be switched
    - **at the low end of the dosing range, ropinirole 0.25 mg ~ pramipexole 0.125 mg**
- Should more strengths of ropinirole and/or pramipexole become unavailable, refer to information below and Table 1 for alternatives.

Parkinson Disease

Non-pharmacological Options[4,5]

- Education/support regarding: exercise, activity, and nutrition; physiotherapy; speech therapy; occupational therapy

Pharmacological Options[4-6]

- See Table 1 for alternative agents and their place in therapy.
- In general, first line agents include levodopa, dopamine agonists and possibly MAO-B inhibitors.
- Almost all patients will require levodopa as disease progresses. Other agents are used as adjuncts: dopamine agonists, MAO-B inhibitors, COMT inhibitors, NMDA antagonists.

Restless Legs Syndrome

Non-pharmacological options[7-9]

- Evidence is lacking for most suggestions below but they are unlikely to be harmful.
- Acute relief may be achieved with stretching/movement.
- Help prevent by: engaging in moderate-intensity exercise; avoiding or limiting alcohol/caffeine/nicotine; activities to occupy mind (RLS may set in during periods of inactivity and boredom); take hot baths; avoid sleep deprivation.
- Discontinue medications that may be causing/exacerbating: antihistamines, antinauseants, antipsychotics, dopamine antagonists, lithium, metoclopramide, selective serotonin reuptake inhibitors, tricyclic antidepressants, calcium channel blockers.

Pharmacological Options[7,8,10]

- A significant number of patients (25-30%) with RLS are iron-deficient. Check iron labs and supplement if deficient though this will not necessarily relieve RLS.
- See Table 1 for alternative agents and their place in therapy.
- In general:
    - levodopa/carbidopa should only be used for intermittent symptoms
    - dopamine agonists are first line when regular treatment is warranted
        - while ergot derivatives may be used, they are not preferred because of their association with pulmonary and cardiac valve fibrosis
    - GABA derivatives are second line
    - several other agents have been used with limited evidence to support

Table 1 – Pharmacological Agents Used for the Treatment of Parkinson Disease and Restless Legs Syndrome

Agent	Use	Initial Dose	Titration	Usual Daily Dose Maximum Daily Dose
Dopamine Agonists				
Non-Ergot Derivatives (High Affinity) **Place in therapy for PD**: **monotherapy for early**; less likely than levodopa to cause fluctuations in early PD but less effective in controlling motor symptoms. **Adjunct to levodopa in late PD**; ↓levodopa off-time and may allow for ↓ levodopa dose (thereby ↓ levodopa-induced dyskinesia)[11] **Place in therapy for RLS**: first line when regular treatment is necessary.[10]				
Ropinirole	PD[4-6]	0.25 mg TID	↑ by 0.25 mg/dose weekly x 4 weeks, then 0.5 mg/dose weekly up to 9 mg/day; then 1 mg/dose up to 24 mg/day	Usual: 1 to 5 mg TID Max: 24 mg
	RLS[7]	0.25 mg 1 to 3 hours before HS	↑ every 4 to 5 nights until effective	Usual: 1 to 4 mg HS
Pramipexole	PD[4-6]	0.125 mg TID	↑ by 0.125 mg/dose q5 to 7 days	Usual: 0.5 to 1.5 mg TID Max: 4.5 mg
	RLS[7,8]	0.125 to 1.5 mg 1 to 3 hours before HS	↑ every 4 to 5 nights until effective	Usual: 0.5 mg HS May need up to 2 mg
Rotigotine	PD[4-6]	Early stage: 2 mg /24 hours once daily Advanced stage: 4 mg/ 24 hours once daily	↑ by 2 mg/24 hours once per week	Usual: 2 to 8 mg/24 hours Max: 16 mg /24 hours
	RLS[7,8]	1 to 3 mg/24 hours once daily HS (does not qualify for EDS)	-	Usual: 1 to 3 mg /24 hours
Ergot Derivatives (Moderate Affinity) – concerns of fibrotic complications/cardiac valvulopathy **Place in therapy for PD:** should **not be used 1st line**; if do use, monitor ESR, renal function, cardiac echocardiogram, chest x-ray at baseline and annually.[11] **Place in therapy for RLS**: cabergoline may be considered 2nd line but not preferred because of adverse effect concerns with higher doses.[10]				
Bromocriptine	PD[4-6]	1.25 mg BID	↑ by 2.5 mg per day q 1-4 weeks	Usual: 5-10 mg TID Max: 30 mg[4] Doses up to 100 mg have been used[6,12]
Cabergoline	PD[6]	0.25 mg daily	↑ q2weeks	Usual: 1 to 3mg once daily Max: 5mg
	RLS[12]	0.5 mg 3 hours before HS	↑ by 0.5 mg q2 to 3 weeks	Usual: 2 to 3 mg HS

Table 1 Continued

Agent	Use	Initial Dose	Titration	Usual Daily Dose Maximum Daily Dose
Dopamine Precursors/Decarboxylation Inhibitors **Place in therapy for PD: monotherapy for early**; keep dose as low as possible to control symptoms without provoking motor complications. **Mainstay for late**: almost all patients will eventually be on levodopa but beneficial effects deteriorate with time (wearing off before next dose, shorter on-phases, unpredictable off-phases, dyskinesias during on-phases – as ↑dose, these dyskinesias ↑)[11] **Place in therapy for RLS:** use levodopa/carbidopa only when intermittent treatment required.[7,8]				
Levodopa/ Carbidopa	PD[5,6]	IR: 50/12.5 mg BID	↑ by 0.5 to 1 tablet q3 to 7 days	Usual: IR: 100/25 mg TID to 250/25 mg TID CR: 200/50 mg BID to QID
	RLS[7,8]	IR or CR: 50/12.5 mg to 100/25 mg HS PRN		Usual: IR or CR: 50/12.5 mg to 200/50 mg HS PRN
Levodopa/ Benserazide	PD[5,6]	50/12.5 mg BID	↑ q3 to 7 days	Usual: 100/25 mg TID to QID
	RLS[7]	50/12.5 mg HS PRN	-	Usual: 50/12.5 mg HS PRN
COMT Inhibitors **Place in therapy for PD: adjunct to levodopa in late**; ↓levodopa off-time[11]				
Entacapone	PD[4-6]	100 to 200 mg with each dose of levodopa	titrate down doses of levodopa as required	Usual: 200 mg TID to QID taken at time of levodopa Max: 1.6 g
Levodopa +Carbidopa + Entacapone	PD[5,6]	Replace previous dosing of levodopa. (1 tablet TID to QID)	↑ as tolerated based on response and presence of dyskinesias	Usual: 1 to 2 tabs TID to QID Max: 8 tablets
Irreversible MAO-B Inhibitors **Place in therapy for PD: may have mild benefits** in early; **adjunct to levodopa in late** – evidence that rasagiline ↓levodopa off-time; such evidence not available for selegiline[11]				
Rasagiline	PD[4,6]	0.5 to 1 mg once daily		Usual: 0.5 mg (adjunct) to 1 mg (monotherapy) once daily Max: 1 mg Max: 0.5 mg if mild hepatic impairment; avoid in severe hepatic impairment
Selegiline	PD[4-6]	2.5 to 5 mg once daily	titrate down the doses of levodopa as needed	Usual: 5 mg once daily to BID Max: 5 mg BID
NMDA Antagonists **Place in therapy for PD: adjunct to levodopa in late** - ↓dyskinesia without worsening parkinsonism. Adverse effects (cognitive, edema) may limit use, especially in older patients.[11]				
Amantadine	PD[4,5,11]	100 mg every other day to 100 mg once daily	↑ by 100 mg/dose q7days	Usual: 100 mg BID to TID Max: 200 mg BID

Table 1 Continued

Agent	Use	Initial Dose	Titration	Usual Daily Dose Maximum Daily Dose
GABA Derivatives **Place in therapy for RLS:** second line[10]				
Gabapentin	RLS[7,8,13]	100 to 300 mg once daily in late afternoon or up to 2 hours before HS	↑ by 100 mg q7 days	Usual: 900 to 1800 mg per day in 2 or 3 divided doses Max: 3600 mg per day
Pregabalin	RLS[8,13]	100 mg once daily, 1 to 3 hours before HS	↑ q2 to 3 days until effective	Usual: 150 to 450 mg daily in 1 or 2 divided doses Max: 450 mg per day
Others				
	PD[4,5]	anticholinergics (benztropine, ethopropazine, trihexyphenidyl); apomorphine; levodopa/carbidopa intrajejunal gel; safinamide		
	RLS[7,8]	amantadine; anticonvulsants (carbamazepine, topiramate; valproic acid); baclofen; clonidine; iron (if deficient); opioids		

BID = twice daily; COMT = catechol-O-methyl transferase; CR= controlled release; EDS = exceptional drug status; ESR = erythrocyte sedimentation rate; GABA= gamma-aminobutyric acid; h= hour; HS= bedtime; IR= immediate release; MAO= monoamine oxidase; Max = maximum; NMDA= N-methyl-D-aspartate; PD=Parkinson Disease; PRN= as needed; q= every; QID= four times daily; RLS= restless legs syndrome; TID = three times daily

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