pad Attention Deficit Hyperactivity Disorder (ADHD) Medications Marketed in Canada for Ages 6 Years and Older (October 2022)

Onset of Effect

- Defined by regulators as a statistically significant difference between drug and placebo on an ADHD symptom scale.[1,2]
- Commonly-prescribed methylphenidate and amphetamine formulations have an onset of effect within hours,[3-7] atomoxetine (Strattera) within 1 to 4 weeks[8] and guanfacine (Intuniv XR) within 1 to 2 weeks.[9]

Dose Response and Titration

- Dose response relationships for ADHD medications are often not well characterized by Health Canada and the US FDA.[1,2]
- ADHD medications are approved with a defined dosage range, informed by fixed-dose trials which typically use rapid or no dose titration and may not apply to clinical practice.[1,2]
- Health Canada advises starting ADHD medications at the lowest dose, then titrating slowly upward to the lowest effective dose; methylphenidate and amphetamines are generally titrated at weekly intervals, atomoxetine (Strattera) at 1 to 2 week intervals, and guanfacine (Intuniv XR) at weekly intervals.[1]

Duration of Effect

- Defined by regulators as the time period for which a change in ADHD symptoms were statistically different from placebo.[1,2]
- Longer-acting methylphenidate and amphetamine formulations have durations that range from ~8 to 16 hours.[4-7,10-13]
- Not reported by Health Canada or the US FDA for immediate release formulations.[10,11,14,15]

Generic Name, Brand Name, available strengths, dosage form, cost, coverage	**ADHD Health Canada Indications, Dosage Considerations** indication, initial dosing, dose response, dose titration, maximum dose, administration, tapering	
METHYLPHENIDATE[1,2,10,11,16,17]		
methylphenidate immediate-release RITALIN, generics 5, 10, 20 mg IR tablets **methylphenidate extended-release** RITALIN SR, generics 20 mg film-coated SR tablets **Cost per 30 Days:** generic: $10 to $30; SR: $10 to $30 brand: discontinued **BC PharmaCare:** Regular Benefit	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ IR tablets: 5 to 10 mg BID or TID with or without food ▪ SR tablets: may be used in place of IR tablets when the 8-hour dosage of SR corresponds to the titrated 8-hour dosage of IR
	Dose Response	▪ not reported by Health Canada, US FDA
	Dose Titration	▪ 5 to 10 mg/day at weekly intervals
	Maximum Dose	▪ 60 mg/day
	Administration	▪ SR tablets: swallow whole, do not crush or chew

Methylphenidate ER Brand and Generic Interchangeability

- Consider cost differences and monitor for changes in effectiveness and adverse events when switching between ADHD medication formulations.
- The US FDA states that for methylphenidate and amphetamines, there is a relationship between drug concentration and efficacy and adverse events; modification to a drug's pharmacokinetics may impact the onset and duration of its effects.[18] It is unclear which specific pharmacokinetic parameter (Cmax, AUC, Tmax) is the most informative and these parameters can show substantial inter-individual variability. For example, the time to maximum concentration for Concerta methylphenidate ER is 6 hours in adults, but varies from 1–10 hours.[12]
- Like several methylphenidate sustained release products, Concerta methylphenidate ER provides a combination of immediate release (IR) and sustained release (SR) properties.[1,12] There are two generic products currently marketed in Canada (APOTEX, Actavis); the manufacturers indicate that the APO generic is only an SR formulation while the ACT generic is a combined IR and SR formulation.[19,20] Small, single-dose bioavailability studies find modest differences in some of the pharmacokinetic parameters between these two generic products and the brand name.[1] We could not find applicable comparisons of these generics to the brand name product examining patient-important outcomes.

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Generic Name, Brand Name, available strengths, dosage form, cost, coverage	**ADHD Health Canada Indications, Dosage Considerations** indication, initial dosing, dose response, dose titration, maximum dose, administration, tapering	
METHYLPHENIDATE[1-5,12,16,17,21-25]		
methylphenidate extended-release CONCERTA, generics 18, 27, 36, 54 mg ER tablets brand name: OROS® in a non-absorbable shell brand name biphasic: IR 22%, ER 78% generic: film-coated tablets **Cost per 30 Days:** generic: $20 to $30 brand: $95 to $150 **BC PharmaCare:** Limited Coverage *brand reimbursed up to the cost of generic*	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ 18 mg once a day in the morning with or without food ▪ switching from IR or SR methylphenidate: see product monograph for dosing ▪ potential for gastrointestinal obstruction: should not be administered to patients with pre-existing gastrointestinal narrowing (obstruction)
	Dose Response	▪ not reported by Health Canada, US FDA
	Dose Titration	▪ at weekly intervals
	Maximum Dose	▪ 54 mg/day (6 to 18 years), 72 mg/day (adults > 18 years)
	Administration	▪ swallow whole with liquids; do not chew, divide or crush
methylphenidate controlled-release BIPHENTIN 10, 15, 20, 30, 40, 50, 60, 80 mg CR capsules multi-layer release (MLR™) beads biphasic: 40% IR, 60% CR **Cost per 30 Days:** generic: not available brand: $30 to $175 **BC PharmaCare:** Non-Benefit	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ 10 to 20 mg once a day in the morning with or without food ▪ switching from another methylphenidate product: reduce dose to next lower strength based on total daily dose (not interchangeable with other CR methylphenidate preparations in Canada)
	Dose Response	▪ not reported by Health Canada, US FDA
	Dose Titration	▪ 10 mg/day at weekly intervals
	Maximum Dose	▪ 60 mg/day (6 to 18 years), 80 mg/day (adults)
	Administration	▪ swallow whole or open capsule and sprinkle onto a tablespoon (15 mL) of applesauce, ice cream or yogurt - consume within 30 minutes; do not sprinkle in liquids, crush or chew
methylphenidate controlled-release FOQUEST 25, 35, 45, 55, **70**$, **85**$, 100 mg CR capsules multi-layer release (MLR®) beads biphasic: 20% IR, 80% CR **Cost per 30 Days:** generic: not available brand: $95 to $160 (70 mg: $135; 85 mg: $145) **BC PharmaCare:** Non-Benefit	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ 25 mg once a day in the morning with or without food ▪ switching from another methylphenidate product: reduce dose to next lower strength based on total daily dose; do not substitute on a mg for mg basis - pharmacokinetic profiles differ
	Dose Response$	▪ US FDA: doses ≥ 70 mg/day in pediatrics and > 85 mg/day in adults are associated with a disproportionate increase in the incidence of adverse events[25]
	Dose Titration	▪ at intervals of no less than 5 days
	Maximum Dose	▪ 70 mg/day (6 to 17 years), 100 mg/day (≥ 18 years) ▪ Health Canada approved a higher maximum dose of Foquest compared to other methylphenidate formulations because it has a lower absorption rate[23]
	Administration	▪ swallow whole or open capsule and sprinkle onto a tablespoon (15 mL) of applesauce, ice cream or yogurt - consume within 10 minutes; do not sprinkle in liquids, crush or chew

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Generic Name, Brand Name, available strengths, dosage form, cost, coverage	**ADHD Health Canada Indications, Dosage Considerations** indication, initial dosing, dose response, dose titration, maximum dose, administration, tapering	
AMPHETAMINES[1,2,6,7,13-17,26-31]		
dextroamphetamine immediate-release DEXEDRINE, generics 5 mg IR tablets **dextroamphetamine sustained-release** DEXEDRINE SPANSULE, generics 10, 15 mg SR capsules pellets, biphasic: 40% IR, 60% SR **Cost per 30 Days:** generic: $10 to $135; SR: $30 to $115 brand: $15 to $205; SR: $40 to $150 **BC PharmaCare:** Regular Benefit *brand reimbursed up to the cost of generic*	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ IR tablets: 2.5 to 5 mg once or twice a day ▪ Spansule: may be used for once a day dosing ▪ ↓ dose and monitor for serotonin toxicity if concomitant use of CYP2D6 inhibitors
	Dose Response	▪ not reported by Health Canada, US FDA
	Dose Titration	▪ 5 mg/day at weekly intervals; give additional IR tablet every 4 to 6 hours
	Maximum	▪ 40 mg/day; only in rare cases will it be necessary to exceed a total of 40 mg/day ▪ ↓ dose if GFR < 30 mL/min/1.73 m^2, dialysis
	Administration	▪ pellets inside Spansule should not be crushed or chewed; opening not expected to compromise SR properties if pellets ingested immediately after opening[26]
amphetamine mixed salts extended-release ADDERALL XR, generics 5, 10, 15, **20**$, 25, 30 mg ER capsules pellets, biphasic: 50% IR, 50% DR 3:1 dextroamphetamine/levoamphetamine salts **Cost per 30 Days:** generic: $20 to $30 (20 mg: $25) brand: $70 to $120 (20 mg: $100) **BC PharmaCare:** Limited Coverage *generic only*	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ 5 to 10 mg once a day in the morning with or without food; food delays Tmax by 2.5 hours, does not affect the extent of absorption ▪ ↓ dose and monitor for serotonin toxicity if concomitant use of CYP2D6 inhibitors
	Dose Response$	▪ Health Canada, US FDA: inadequate evidence of additional efficacy for doses > 20 mg/day in adolescents and adults[7,27]
	Dose Titration	▪ 5 to 10 mg/day at weekly intervals
	Maximum Dose	▪ 30 mg/day ▪ ↓ dose if GFR < 30 mL/min/1.73 m^2 to a maximum of 20 mg/day; further reduce in dialysis
	Administration	▪ contents may be sprinkled onto applesauce - consume immediately; do not crush or chew
lisdexamfetamine VYVANSE 10, 20, **30**$, 40, 50, 60 mg capsules 10, 20, **30**$, 40, 50, 60 mg chewable tablets **Cost per 30 Days:** generic: not available brand: $90 to $160 (30 mg: $105) **BC Pharmacare:** Limited Coverage *capsules only*	**Indication**	▪ ADHD: ages ≥ 6 years
	Initial Dosing	▪ 20 to 30 mg once a day in the morning with or without food; food delays Tmax by ~1 hour, does not affect the extent of absorption ▪ ↓ dose and monitor for serotonin toxicity if concomitant use of CYP2D6 inhibitors
	Dose Response$	▪ Health Canada, US FDA: efficacy does not meaningfully increase at doses > 30 mg/day but adverse events and discontinuations were more frequent at higher doses[6,30,31]
	Dose Titration	▪ 10 to 20 mg/day at weekly intervals
	Maximum Dose	▪ 60 mg/day ▪ ↓ dose if GFR < 30 mL/min/1.73 m^2 to a maximum of 50 mg/day; further reduce in dialysis
	Administration	▪ capsules: contents may be mixed with yogurt, water or orange juice - consume immediately ▪ chewable tablets: chew thoroughly before swallowing; should not be divided

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<table>
<tr><th>Generic Name, Brand Name, available strengths, dosage form, cost, coverage</th><th colspan="2">ADHD Health Canada Indications, Dosage Considerations
indication, initial dosing, dose response, dose titration, maximum dose, administration, tapering</th></tr>
<tr><td colspan="3">ATOMOXETINE[1,2,8,17,18,32]</td></tr>
<tr><td rowspan="6">atomoxetine
STRATTERA, generics
10, 18, 25, 40, 60, 80, 100 mg capsules

Cost per 30 Days:
generic: $20 to $45
brand: $105 to $195

BC PharmaCare: Limited Coverage
generic only</td><td>Indication</td><td>▪ ADHD: ages ≥ 6 years; not officially indicated for use in combination with psychostimulants</td></tr>
<tr><td>Initial Dosing</td><td>▪ ~0.5 mg/kg/day (Step 1) for 7 to 14 days; body weight should be at least 20 kg
▪ take as a single daily dose in the morning or divided BID, with or without food
▪ ↓ initial and target doses in moderate to severe hepatic impairment (Child-Pugh Class B: reduce to 50%; Child-Pugh Class C: reduce to 25% of normal dose)

<table><tr><th>Body Weight</th><th>Step 1 (~0.5 mg/kg/day)</th></tr><tr><td>20 to 29 kg</td><td>10 mg/day</td></tr><tr><td>30 to 44 kg</td><td>18 mg/day</td></tr><tr><td>45 to 64 kg</td><td>25 mg/day</td></tr><tr><td>> 65 kg</td><td>40 mg/day</td></tr></table></td></tr>
<tr><td>Dose Response</td><td>▪ Health Canada, US FDA: maximal effect at 1.2 mg/kg/day in children and adolescents ≤ 70 kg[8,32]</td></tr>
<tr><td>Dose Titration</td><td>▪ if tolerated, increase to Step 2 for 7 to 14 days, and then to Step 3 for 30 days (2 to 4 weeks if > 70 kg), reassess
▪ ↓ dose if concomitant strong CYP2D6 inhibitor (increase from initial dose only if symptoms fail to improve after 14 days and initial dose well tolerated)

<table><tr><th>Body Weight</th><th>Step 2 (~0.8 mg/kg/day)</th><th>Step 3 (~1.2 mg/kg/day)</th></tr><tr><td>20 to 29 kg</td><td>18 mg/day</td><td>25 mg/day</td></tr><tr><td>30 to 44 kg</td><td>25 mg/day</td><td>40 mg/day</td></tr><tr><td>45 to 64 kg</td><td>40 mg/day</td><td>60 mg/day</td></tr><tr><td>> 65 kg</td><td>60 mg/day</td><td>80 mg/day</td></tr></table></td></tr>
<tr><td>Maximum Dose</td><td>▪ 1.4 mg/kg/day or 100 mg/day, whichever is less</td></tr>
<tr><td>Administration</td><td>▪ do not open capsule, swallow whole</td></tr>
</table>

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<table>
<tr><th>Generic Name, Brand Name, available strengths, dosage form, cost, coverage</th><th colspan="3">ADHD Health Canada Indications, Dosage Considerations
indication, initial dosing, dose response, dose titration, maximum dose, administration, tapering</th></tr>
<tr><td colspan="4">GUANFACINE[1,2,9,13,16,17,33-35]</td></tr>
<tr><td rowspan="7">guanfacine extended-release
INTUNIV XR, generics
1, 2, 3, 4 mg tablets

Cost per 30 Days:
generic: $85 to $260
brand: $100 to $310

BC PharmaCare: Non-Benefit</td><td>Indications</td><td colspan="2">▪ ADHD monotherapy: ages 6 to 17 years
▪ ADHD adjunct to psychostimulants: ages 6 to 17 years
▪ safety and efficacy not established in children < 25 kg</td></tr>
<tr><td>Initial Dosing</td><td colspan="2">▪ 1 mg once a day in the morning or evening with a small amount of liquid
▪ do not take with high-fat meal: increases mean exposure (AUC ~40% and Cmax ~75%)
▪ do not take grapefruit, grapefruit juice or grapefruit extract during treatment with guanfacine</td></tr>
<tr><td>Dose Response</td><td colspan="2">▪ Health Canada, US FDA: efficacy and sedative adverse events (somnolence, sedation, hypersomnia, fatigue, lethargy, asthenia) increase with dose[9,33-35]</td></tr>
<tr><td>Dose Titration</td><td>▪ by no more than 1 mg/week
▪ target dose range: 0.05 to 0.12 mg/kg/day
▪ monitor blood pressure, heart rate and for sedation</td><td><table><tr><th>Body Weight</th><th>Target Dose Range</th></tr><tr><td>25 to 33.9 kg</td><td>2 to 3 mg/day</td></tr><tr><td>34 to 41.4 kg</td><td>2 to 4 mg/day</td></tr><tr><td>41.5 to 49.4 kg</td><td>3 to 5 mg/day</td></tr><tr><td>49.5 to 58.4 kg</td><td>3 to 6 mg/day</td></tr><tr><td>≥ 58.5 kg</td><td>4 to 7 mg/day</td></tr></table></td></tr>
<tr><td>Maximum Dose</td><td colspan="2">▪ monotherapy: 4 mg/day (6 to 12 years), 7 mg/day (13 to 17 years); adjunct: 4 mg/day
▪ ↓ dose if significant renal and/or hepatic impairment
▪ ↓ dose if concomitant use of moderate/strong CYP3A4/3A5 inhibitors (initial 50% reduction)
▪ ↑ dose if concomitant use of strong CYP3A4 inducers (up to a maximum of 7 mg)</td></tr>
<tr><td>Administration</td><td colspan="2">▪ swallow whole; do not crush, chew or break</td></tr>
<tr><td>Tapering</td><td colspan="2">▪ avoid abrupt withdrawal: risk of increase in blood pressure and heart rate (rebound)
▪ taper total daily dose by no more than 1 mg every 3 to 7 days
▪ monitor blood pressure and heart rate when initiating, increasing the dose, reducing the dose or discontinuing the drug
▪ use caution in prescribing other medications (e.g., stimulants) that can elevate blood pressure and heart rate immediately following guanfacine discontinuation</td></tr>
<tr><td colspan="4">US FDA: United States Food and Drug Administration; IR: immediate release; SR: sustained release; BID: twice a day; TID: three times a day; Cmax: maximum plasma concentration; AUC: area under the curve; Tmax: time to maximum observed plasma concentration; ER/XR: extended release; OROS®: Osmotic Controlled-Release Oral Delivery system; CR: controlled release; CYP: Cytochrome P450; GFR: glomerular filtration rate; DR: delayed release; principal source of information: regulatory reviews and prescribing information from Health Canada and the US Food and Drug Administration</td></tr>
<tr><td colspan="4">Cost per 30 days: does not include mark-up or professional fee; provided as a range which includes approximate cost for initial to maximum doses calculated from McKesson Canada, Aug 17, 2022.</td></tr>
</table>

Management of Suspected Drug Overdose → Contact the British Columbia Drug and Poison Information Centre (DPIC)

http://www.dpic.org/

24 Hour Poison Information Line: 1-800-567-8911 or 604-682-5050

Drug Information Line for BC Healthcare Professionals Only: 1-866-298-5909 or 604-707-2787 (Monday to Friday, 9 am to 4 pm)

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