

Extended-release methylphenidate (Concerta) for attention deficit hyperactivity disorder

(meth-il-FEN-i-date)


Summary


- Extended-release methylphenidate (Concerta) is one of two available controlled-release formulations of the psychostimulant methylphenidate (immediate-release methylphenidate is commonly known by the brand name Ritalin; the other controlled-release formulation is Ritalin-LA).
- The efficacy of extended-release methylphenidate is similar to that of immediate-release methylphenidate.
- Extended-release preparations eliminate the need for medicine use at school, which may be stigmatising, is difficult to enforce and carries the potential of diversion for illicit use.
- Individualise dose using immediate-release methylphenidate then switch to an equivalent dose of the controlled-release formulation.
- This once-daily extended-release formulation is equivalent to three-times-daily dosing with immediate-release methylphenidate. It may not be suitable for children who require less than 12 hours coverage or a more tailored daily regimen.
- Treatment should be based on a comprehensive diagnosis and employ behavioural, psychosocial and educational strategies according to individual needs.
- Be aware of potential cardiovascular adverse effects with psychostimulants; do not use in children with structural cardiac abnormalities, serious heart problems or those with conditions that may be exacerbated by increased pulse rate or blood pressure.

PBS listing

Authority required

Treatment of attention deficit hyperactivity disorder (ADHD) in a child or adolescent aged 6–18 years inclusive, who has demonstrated a response to immediate-release methylphenidate hydrochloride with no emergence of serious adverse events, and who requires continuous coverage over 12 hours.

Adhere to State and Territory regulations when prescribing psychostimulants. [www](#) 

[www](#)  Refer to this review at www.npsradar.org.au for contact details of the relevant State and Territory authorities.

Reason for PBS listing

Extended-release methylphenidate was listed on the basis of cost-effectiveness compared with the immediate-release formulation.¹ The initial submission claimed greater effectiveness than immediate-release methylphenidate, but the Pharmaceutical Benefits Advisory Committee (PBAC) found inadequate evidence of this and uncertain and unacceptable cost-effectiveness at the price proposed, and rejected the submission.^{2,3} A subsequent application at a new price was approved; although the extent of any clinical benefit over immediate-release methylphenidate remains uncertain, the PBAC agreed that the possible benefits in compliance and ease of administration, particularly in relation to the removal of the need for a dose of medication at school, were sufficient to justify listing.³

Place in therapy

When drugs are required for managing ADHD, the psychostimulants methylphenidate and dexamphetamine are first line, combined with non-drug interventions according to individual needs.^{4,5} Dexamphetamine and methylphenidate are considered to have similar effectiveness relative to placebo. There is insufficient evidence comparing these drugs to conclude that either is better, but individuals may respond better to one or the other.^{4,6,7} Similarly, the efficacy of atomoxetine (a non-stimulant) compared with that of psychostimulants is uncertain⁴; it should be considered second line to psychostimulants.

Methylphenidate immediate-release formulations have a short half-life, and 2 or 3 daily doses are usually required. Controlled-release preparations can be given once daily, which could improve compliance by eliminating the need for medicine use at school. However, the available doses may not suit all children and immediate-release formulations may allow greater flexibility in dosing regimens.⁷ (See Dosing issues)

Long-term prescribing of psychostimulant medications to children for purely symptomatic control raises some concerns, and it is important to^{4,5,8}:

- base prescribing and management on a comprehensive specialist diagnosis and assessment
- individualise the dose, taking note of teacher and parental reports; monitor frequently
- use the minimum dose, frequency and duration that controls symptoms
- stop treatment if there is no response after 1 month of optimal treatment
- review the need for ongoing therapy at least annually. As part of this review, try drug-free periods of 1–2 weeks to assess if medication is still needed, when and if individual circumstances allow it. While teachers' reports of the child's behaviour on and off medication are integral to assessing the ongoing need for medication, a trial off medication during school holidays may be easier as a first step.

Efficacy is similar to that of immediate-release formulations

No difference in efficacy was found between immediate-release methylphenidate and the controlled-release preparation (Concerta) in randomised blinded trials; both reduced symptoms more than placebo.⁹⁻¹¹ The only trial to demonstrate a benefit was an unblinded effectiveness trial that aimed to identify whether once daily dosing was more effective than three-times-daily dosing.

This trial probably overestimates treatment effects because of its unblinded nature and sole reliance on parental ratings of ADHD symptoms as a measure of improvement. Symptom ratings improved more with the controlled-release formulation than the immediate-release formulation; however, parent stress was lower with the controlled-release preparation, which may have influenced their symptom ratings.

Equivalent to immediate-release methylphenidate three doses per day

Concerta is appropriate for children who usually have three doses of immediate-release methylphenidate per day. A once-daily dose of Concerta provides around 12 hours coverage and is equivalent to a three-times-daily dose regimen of immediate-release methylphenidate.^{4,12,13} A once-daily dose of Ritalin LA (the other controlled-release methylphenidate preparation available in Australia) provides about 8 hours coverage and is equivalent to immediate-release methylphenidate administered twice daily. Ritalin LA is not PBS listed.

The two formulations have different release profiles that result in their different durations of effect. Ritalin LA capsules contain half the dose as immediate-release beads and half as delayed-release beads.¹² Concerta tablets are composed of an external layer of immediate-release methylphenidate and two internal layers from which the drug is gradually released.¹³

Assess and treat individual needs across multiple domains of functioning

Despite a lack of supporting evidence, consensus guidelines recommend that children receive multi-dimensional treatment for ADHD, involving the child, parents and teachers.^{5,14} Depending on the child's individual situation, consider options including behavioural management, family education and support (e.g. respite), and developmental or educational interventions, concurrent with medication. Because there is little evidence that drug therapy has long-term benefits on academic performance, educational support is particularly important.⁵

Combining intensive behavioural interventions with careful medication management did not reduce core ADHD symptoms (inattention, impulsivity) any more than medication alone in the 14-month independently funded MTA study.¹⁵ Nonetheless:

- medication needs were reduced in children on combined drug-behavioural therapy.¹⁵
- combined therapy improved some aspects of social functioning, for example, oppositional/aggressive behaviour, internalising symptoms, social skills and parent-child relationships, which did not improve with medication alone.¹⁴

Safety issues

As with other psychostimulants:

- common adverse effects include anorexia, weight loss, abdominal pains, insomnia, headaches and anxiety.^{6,13}
- monitor weight and height — while some growth retardation is possible, in most cases this will be insignificant in the long term.⁵

Extended-release methylphenidate has been associated with stuttering priapism (intermittent but sustained painful erections) during short breaks in treatment in 2 published case reports^{16,17} with a further 8 reports to the manufacturer between 2000 and 2006.¹⁸ In the published cases the boys delayed reporting their symptoms for several months because of embarrassment. Although very rare, it may be worth informing boys and their parents of this potential adverse effect because of the likelihood of under-reporting and its possible long-term consequences.

Safety and efficacy for use in children under 6 years of age has not been established.¹³

Be aware of potential cardiovascular adverse effects

Concerns about cardiovascular safety (and psychiatric adverse effects) with psychostimulant use in children were reviewed by the US Food and Drug Administration (FDA) in 2006.¹⁹⁻²² The Therapeutic Goods Administration has conducted a similar review.

The cardiovascular events reviewed included instances of sudden death, non-fatal cardiovascular events and cerebrovascular adverse events. In most cases of sudden death, a previously undiagnosed cardiac problem was present.²¹ The Concerta product information warns that sudden death may occur in children and adults with structural cardiac abnormalities or other serious heart problems.¹³

Prescribers are advised to:

- obtain a personal and family cardiac history before prescribing extended-release methylphenidate (or other psychostimulants). Avoid use in patients who have:
 - known structural cardiac abnormalities or
 - serious heart problems (e.g. cardiomyopathy, arrhythmias) or
 - conditions that may be exacerbated by increased pulse rate or blood pressure.¹³
- refer for cardiologist assessment before prescribing to patients with the above conditions, hypertension or a family history of sudden death or syncope or other relevant cardiac disease.^{6,13}
- measure pulse and blood pressure at baseline, after dose increases and periodically.⁶
- promptly evaluate patients who develop exertional chest pain, unexplained syncope or other symptoms of cardiovascular disease.¹³

Both immediate-release and extended-release methylphenidate increase blood pressure (by 1–4 mmHg) and heart rate (by 2–6 beats/min) during use.^{13,19,23} The long-term implications of a sustained increase in heart rate and blood pressure in children with normal heart function is unknown.

Psychiatric adverse effects and comorbidity

Psychiatric adverse-event reports in the FDA review included psychosis (for example, visual and tactile hallucinations in young children), mania, aggression and suicidal ideation.^{20*} These conditions may be precipitated or worsened by psychostimulants. Similarly, depression and anxiety may be treatment-related adverse effects or be present comorbidly.

Seek specialist advice, particularly before prescribing an antidepressant (or other psychotropic drug) concurrently with methylphenidate, because of possible additive cardiovascular adverse effects⁸ and the risk of serotonin syndrome.²⁴ Monoamine oxidase inhibitors are contraindicated with methylphenidate; avoid moclobemide.⁶

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with Australian Prescriber. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Dosing issues

- Methylphenidate extended-release tablets should be taken once daily in the morning.¹³
- Use immediate-release methylphenidate to titrate to an effective and tolerated dose before switching to an equivalent dose of the controlled-release preparation. Doses can be increased at weekly increments.¹³
- Follow up regularly (for example, monthly) to monitor dose.
- Available doses of controlled-release formulations may not suit all children^{6,7}; there may not be an equivalent dose of the controlled-release

formulation for all immediate-release dose regimens. For example, some children could require a high dose in the morning and a lower dose in the late afternoon.

- When switching from the immediate-release preparation, use the nearest equivalent dose. For example, for methylphenidate immediate-release up to 15 mg daily, use Concerta 18 mg; for methylphenidate immediate-release 20–30 mg daily, use Concerta 36 mg.⁶
- In very obese children, ideal weight should be used to estimate drug dosage.⁵
- The tablet is a large non-deformable tablet that must be swallowed whole. It can cause gastrointestinal obstruction in patients with existing narrowing of the gastrointestinal tract. The tablet casing is excreted intact in the faeces.¹³

Information for patients

Inform patients:

- that Concerta is a substitute for their previous psychostimulant
- to swallow the tablet whole and not to split it
- that the tablet casing is excreted in faeces (this is sometimes a cause for concern).

Advise patients and carers of both common adverse effects and rare but significant adverse effects, and to report any symptoms of these including:

- cardiovascular adverse effects (e.g. exertional syncope, palpitations, fast heart beat, increased blood pressure)
- psychiatric adverse effects (e.g. aggression, unusual thoughts, changes in mood including anxiety, agitation, depression).
- priapism.

Reassure patients that long-term effects on growth or weight are unlikely, but that height and weight should be monitored and compared to expected growth.

Suggest or provide the Concerta consumer medicine information (CMI) leaflet.

*The nature of adverse events data and the low rate of incidents overall means that causality for suicidal ideation could not be established

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.