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New drugs

Mirabegron

Approved indication: overactive bladder
Betmiga (Astellas)
25 mg and 50 mg film-coated tablets
Australian Medicines Handbook section 13.1

People with overactive bladder have urgency with or without frequency and nocturia. Antimuscarinics such as oxybutynin, tolterodine, solifenacin (Aust Prescr 2006;29:138-43) and darifenacin are the mainstay of drug treatment (Aust Prescr 2014;37:10-3). They are often used in conjunction with bladder training.

Mirabegron is an agonist of beta$_3$ adrenergic receptors. It works by activating these receptors in the detrusor muscle of the bladder. This relaxes the muscle and increases bladder capacity.

The safety and efficacy of mirabegron has been evaluated in three placebo-controlled, 12-week studies.[1-3] A pooled analysis of the trials found that once-daily 50 mg and 100 mg doses statistically improved incontinence and micturition frequency (see Table).[4] However, there was no dose–response effect. The mean number of incontinence episodes per day fell by 1.48 with mirabegron 50 mg and by 1.54 with the 100 mg dose. Incontinence episodes fell by 1.09 a day with placebo. Although an active control was included in one of the trials (extended-release tolterodine), a statistical comparison with mirabegron was not reported.[2]

The most common adverse effects with mirabegron and placebo included hypertension (7.3% vs 7.6% of participants), nasopharyngitis (3.4% vs 2.5%), urinary tract infection (3% vs 1.8%), headache (2.9% vs 3.1%), dry mouth (2% vs 2.1%) and constipation (1.6% vs 1.4%).[4] Tachycardia was common, occurring in 1.2% of people taking mirabegron 50 mg. Palpitations and atrial fibrillation have also been reported. Blood pressure monitoring is recommended, especially in patients with hypertension, and mirabegron is not recommended in uncontrolled hypertension. Caution is urged in those who may have a prolonged QT interval.

In a long-term extension study of safety (52 weeks), 11 of 820 people who received mirabegron 100 mg had a neoplasm (benign or malignant). Only 1 of 812 people reported a neoplasm with mirabegron 50 mg and 4 of 812 people who received tolterodine.

Following an oral dose, mirabegron reaches peak plasma concentrations after 3–4 hours. Steady-state concentrations are achieved after seven days. The terminal half-life is approximately 50 hours and the drug is eliminated in the urine (55%) and faeces (34%). This drug is not recommended in patients with end-stage renal disease or severe hepatic impairment.

In animal studies, mirabegron has shown reproductive toxicity and is excreted in milk. It is therefore not recommended in pregnancy or lactation.

Mirabegron is transported and metabolised by multiple pathways so there is potential for drug interactions. Monitoring and dose adjustment may be needed with concomitant drugs that are extensively metabolised by CYP2D6 and have a narrow therapeutic index, such as flecainide and imipramine. Mirabegron also increases exposure to concomitant digoxin so digoxin should be started at a low dose and titrated based on serum concentrations.

Mirabegron is indicated for urgency, increased micturition frequency and urgency incontinence in adults with overactive bladder. It showed only modest efficacy in the trials with the average number of incontinence episodes being reduced by around 1.5 a day. This was compared to people given placebo

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table **Efficacy of once-daily mirabegron 50 mg and 100 mg from a pooled analysis[4] of three phase III trials [1-3]**

Intervention	Total number of patients	Mean number of incontinence episodes/24 hours‡		Mean number of micturitions/24 hours	
		baseline	12 weeks	baseline	12 weeks
placebo	1328	2.73	1.64	11.58	10.39
mirabegron 50 mg	1324	2.71	1.23	11.70	9.93
mirabegron 100 mg	890	2.79	1.25	11.58	9.83

‡ included only patients who reported ≥1 incontinence episode at baseline (858 patients for placebo, 834 for mirabegron 50 mg, 567 for mirabegron 100 mg)

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who had approximately 1.1 fewer incontinence episodes a day. Currently, there are limited comparative and long-term efficacy data with this drug. In the UK[5], mirabegron is only recommended when antimuscarinic drugs are contraindicated, ineffective or not tolerated.

T T manufacturer provided additional useful information

REFERENCES *†

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2. Khullar V, Amarenco G, Angulo JC, Cambronero J, Hoye K, Milson I, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol 2013;63:283-95.
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5. Mirabegron for treating symptoms of overactive bladder. National Institute for Health and Care Excellence. 2013.

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).