Mirabegron

▼Betmiga® for overactive bladder syndrome Irrelevant benefits

Indications[1]
Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Mechanism of action and pharmacokinetics[1,2]
It is a selective beta 3 adrenergic agonist that relaxes the bladder's smooth muscle. It binds to plasma proteins (71%). The elimination half-life of this drug is approximately 50 h. Elimination occurs in 55% in urine (25% unaltered) and 34% through faeces.

Posology and administration[1]
The recommended dose is 50 mg once daily with or without food. The tablet should be taken with liquid and should be swallowed entirely and not be chewed, split or crushed in powder form.

Clinical efficacy
Approval of mirabegron was based on 3 placebo-controlled, double-blind trials of 12 week duration. The primary endpoints were the same[2]: change in the average number of episodes of incontinence during a 24 hour period, and the change in the number of micturitions in 24 hours.

The number of patients included in the 3 trials was 4622 (women 72-83%). The average age was approximately 60 years (38%≥65 years) and the average BMI was between 27.8 and 30.2 kg/m². Participants presented an average of 11-12 micturions per day and 2 to 3 incontinence episodes. Not all patients included were incontinent (59%[3,5] and 70%[4]). The clinical trials compared mirabegron 25, 50 and 100 mg to placebo. One of them included an active control (tolterodine 5 mg) but the results comparing tolterodine with mirabegron were not published.[3]

Mirabegron does not even reduce one **incontinence episode** during the day compared to placebo. With regard to the number of **daily micturitions** *vs* placebo, it does not even reduce at least one more micturition in patients with an average of 11-12 micturitions in 24 h.[3-4]

A 12-month study on 2452 patients compared three treatment arms, mirabegron 50 mg and 100 mg, and tolterodine SR 4 mg.[6] The reduction in the number of episodes of **incontinence** in 24 h was 1.01 for mirabegron 50 mg and 1.26 for tolterodine. The change in the number of **daily micturitions** was -1.27 with mirabegron 50 mg and -1.39 with tolterodine.

Safety
Adverse reactions[1]
The most frequent adverse reactions reported were tachycardia (1.2%) and urinary tract infections (2.9%). Among the severe adverse reactions we find atrial fibrillation (0.2%).[1]

During the 12-month trial[6] the most frequent adverse reactions among the groups were similar except for dry mouth syndrome (8.6% under tolterodine *vs* 2-8% under mirabegron 50 mg). Severe adverse reactions were reported in 5.2% of the patients under mirabegron 50 mg and 5.4% under tolterodine. Withdrawal due to adverse reactions ocurred in 6.4% and 6.0% patients, mirabegron 50 mg and tolterodine, respectively.

Little efficacy, similar to anticholinergic agents

Contraindications[1]
Hypersensitivity to the main substance or any of its excipients.

Warnings and precautions[1]
Hypertension. It is not recommended in patient with uncontrolled severe hypertension. The data are limited in patients with stage 2 hypertension.
Patients with prolonged QT interval. Precaution should be taken in patients with a history of long QT syndrome or under treatment with drugs that prolong the QT interval

Use in special situations[1]
Pregnancy and lactation: not recommended.
Renal impairment: not recommended in cases of terminal renal failure. In severe renal failure the recommended dose is 25 mg (not marketed, while the 50 mg tablets cannot be split) and it should not be used with any potent CYP3A inhibitor. **Liver failure (LF):** In *severe* cases it is not recommended. In *moderate* liver impairment the recommended dose is 25 mg and it should not be used along with any potent CYP3A inhibitor. In patients with **mild** liver impairment the dose should be reduced to 25 mg. **Children:** no available data in patients under 18 years.

Interactions[1]
In patients under therapy with potent CYP3A inhibitors (itraconazole, ketoconazole, ritonavir, clarithromycin) and mild renal failure or mild liver failure the recommended dose is 25 mg

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ABSTRACT

Mirabegron is the first selective beta 3 adrenergic receptor agonist.

Its efficacy is similar to that of anticholinergic drugs. There is a high response to placebo. The absolute improvement with mirabegron is very small and clinically irrelevant.

It produces less dry mouth syndrome than tolterodine but there are no differences in treatment withdrawal due to adverse effects. Tachycardia and urinary infections are the most frequent adverse effects. Its long-term safety profile is unknown.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

Table 1. Results of the clinical trials.

	KHULLAR V[3]			NITTI VW[4]		HERSCHORN S[5]	
	PLACEBO	MIRABEGRON 50 MG	TOLTERODINE SR 4 MG	PLACEBO	MIRABEGRON 50 MG	PLACEBO	MIRABEGRON 50 MG
Change in the average number of incontinence episodes in 24 h	-1.17 (-1.39 to -0.95)	-1.57 (-1.79 to -1.35)	-1.27 (-1.49 to -1.05)	-1.13 (-1.35 to -0.91)	-1.47 (-1.69 to -1.25)	-0.96 (-1.19 to -0.72)	-1.38 (-1.62 to -1.14)
Average change in the number of micturitons in 24 h	-1.34 (-1.12 to -1.55)	-1.93 (-2.15 to -1.72)	-1.59 (-1.80 to -1.37)	-1,05 (-1.31 to -0.79)	-1.66 (-1.92 to -1.40)	-1.18 (-1.42 to -0.94)	-1.60 (-1.84 to -1.36)
Change in average urine volume (mL)	12.3 (8.4 to 16.3)	24.2 (20.3 to 28.2)	25.0 (21.1 to 28.9)	7,0 (2.3 to 11.7)	18.2 (13.4 to 22.9)	8.3	20.7

daily. It is not recommended in patients with severe renal failure or moderate liver failure.

Precaution is recommended when administered concommitantly with drugs that present a narrow therapeutic range and are metabolized via CYP2D6 (tioridazine, flecainide, propafenone, imiprmine, desipramine).

Mirabegron is a weak P-gp inhibitor. When administered with digoxin (a P-gp substrate), initially the lowest possible dose of the latter should be prescribed and plasma levels monitored to make dose adjustments. Other possible interactions with P-gp sensitive substrates like dabigatran should be taken into account.

The increase in mirabegron plasma levels due to pharmacological interactions could be associated with increases in pulse rate.

EMA Risk Management Plan[1]

This includes two important risks identified (increase in heart rate and tachycardia, and hypersensitivity reactions) and 5 important potential risks (prolonged QT interval, hypertension, urinary tract infections, fetal-embryo toxicity and concommitant therapy with CYP2D6 substrates with narrow therapeutic range).

Place in therapeutics

Initial therapy for all patients with urinary incontinence include lifestyle changes and behavioural therapy (bladder training, pelvis muscle training exercises). The latter can be as effective as pharmacological treatment for urgent incontinence. Behavioural therapy should be maintained at least for 3 months before pharmacological treatment is considered.[9]

Mirabegron is the first beta 3 adrenergic agonist. Trials carried out on this drug are of short duration. There are no available data on long-term efficacy. The high patient response to placebo is such that the overall improvement with mirabregon is very small and clinically irrelevant. In clinical trials studying mirabegron there was no reduction in episodes of daily incontinence with respect to placebo while the number of daily micturitions decreased in less than one micturition *vs* placebo in patients with an average of 11-12 micturitions per day.

There are no comparative trials with anticholinergic agents. There seems to be no difference in efficacy. However, while their adverse effects profile is somewhat different they are not better. Mirabegron produces less dry mouth than tolterodine but there are no differences in treatment withdrawal due to adverse effects. Unlike anticholinergic drugs, precaution should be taken when administering mirabregon with drugs metabolized through CYP2DA presenting a narrow therapeutic range.

In any case, its effect is clinically irrelevant. In addition, if we take into account the heart risks and possible urinary infections, along with the uncertainty on its long-term safety profile its use is hard to justify.

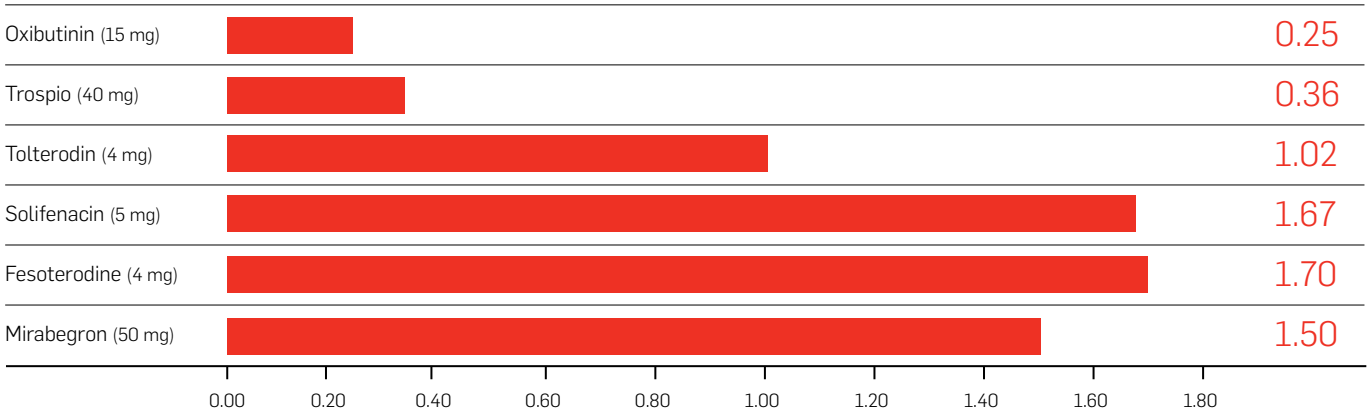
Presentations

Betmiga® (Laboratory) 50 mg 30 prolonged release tablets (45.12 €)

References

A complete report on mirabegron can be found at: http://www.bit.navarra.es

DAILY COST OF TREATMENT (€)



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