HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
23 July 2014

BETMIGA 25 mg, prolonged-release tablet
B/30 (CIP: 34 009 273 182-5 2)
BETMIGA 50 mg, prolonged-release tablet
B/30 (CIP: 34 009 273 183-1 3)

Applicant: ASTELLAS PHARMA SAS

INN	mirabegron
ATC Code (2013)	G04BD12 (urinary antispasmodic)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome."**

Actual Benefit	**"Symptomatic treatment of urgency and increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome (OAB).** **This actual benefit is provisional pending the results of the study versus solifenacin (VESICARE).**
Improvement in Actual Benefit	**In view of:** - **the weak efficacy observed versus the placebo, particularly in terms of reducing daily micturition frequency,** - **the limitations of the evaluation (exploratory quality of life data, absence of an evaluation *versus* anticholinergic drugs in treatment-naive patients, absence of direct comparisons versus therapeutic alternatives),** - **the data available, and notably the indirect comparison which does not enable a distinction between BETMIGA and anticholinergic drugs nor the ranking of treatments in relation to one other,** **no conclusion regarding comparative efficacy can be formulated and the therapeutic advances procured by BETMIGA are difficult to assess by comparison with existing alternative medicinal products (anticholinergic drugs) with the same indication.** **The Committee therefore considers that BETMIGA does not procure an improvement in actual benefit (level V, non-existent) in the symptomatic treatment of urgency and increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome and, in particular, pending the results of the study versus solifenacin (VESICARE).**
Therapeutic Use	**The role of BETMIGA in therapeutic strategy is difficult to specify in light of the data available and the absence of studies versus anticholinergic drugs. It is left to the discretion of prescribing practitioners.**
Recommendations	**The Committee will re-assess its conclusions in light of new data, in particular comparative data versus anticholinergic drugs (a study is ongoing in patients in whom an anticholinergic drugother than VESICARE was ineffective).**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date (centralised procedure): 20 December 2012
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	G	Genito urinary system and sex hormones
	G04	Urologicals
	G04B	Urologicals
	G04BD	Drugs for urinary frequency and incontinence
	G04BD12	mirabegron

02 BACKGROUND

Mirabegron (BETMIGA) is a potent and selective beta 3-adrenoceptor agonist. It is not an anticholinergic agent.
It is the first representative of a new class of drugs for the treatment of urinary incontinence in patients with overactive bladder. Whilst the stimulation of bladder muscarinic receptors by anticholinergic drugs promotes micturition, the activation of beta adrenoceptors facilitates urine storage in the bladder by producing detrusor muscle relaxation during the bladder storage phase, thus increasing the bladder capacity.

The Transparency Committee re-assessed the Actual Benefit (AB), Improvement in Actual Benefit (IAB) and the target population of all anticholinergic drugs indicated in the treatment of urinary incontinence, namely DITROPAN, CERIS, VESICARE and TOVIAZ in response to a referral by the Healthcare Products Pricing Committee in November 2012.
After an analysis of the literature, obtaining opinions from experts and consultations with learned societies, it is apparent to the Committee that in terms of AB, no distinction could be made between the four anticholinergic drugs, despite their modest efficacy (reduction in daily micturition frequency of around one micturition when compared with a placebo). These proprietary medicinal products remain the reference drug therapy for urinary incontinence without any preferential recommendation of one over another.

In its opinion issued on 26 June 2013, the conclusions of the TC were as follows:

- the actual benefit of the proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ **remains moderate** in the symptomatic treatment of urgency incontinence and/or increased micturition frequency and/or urgency in adult patients with overactive bladder.
  Nevertheless, the efficacy/adverse effects ratio of DITROPAN (classified as low) was distinct from that of the other three anticholinergic drugs (classified as moderate) because oxybutynin, administered at high doses of more than 10 mg/day, particularly in elderly patients, is associated with a less favourable safety profile.

- the proprietary medicinal products CERIS, VESICARE and TOVIAZ procure a minor improvement in actual benefit (**level IV), in terms of safety when compared to DITROPAN**, in the symptomatic treatment of urgency incontinence and/or increased micturition frequency and urgency in adult patients with overactive bladder, given the comparable efficacy between the four anticholinergic drugs, the better safety profiles of CERIS, VESICARE and TOVIAZ versus DITROPAN as supported by recent international guidelines and metaanalyses of good methodological quality, the absence of data enabling a distinction between CERIS, VESICARE and TOVIAZ in terms of clinical performance and the mediocre safety profile of DITROPAN, particularly in elderly patients, which raises concerns.

03 THERAPEUTIC INDICATIONS

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

04 DOSAGE

"Adults (including elderly patients)
The recommended dose is 50 mg once daily with or without food.

Special populations
Renal and hepatic impairment
BETMIGA has not been studied in patients with end stage renal disease (GFR < 15 ml/min/1.73 m^2 or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see sections 4.4, 4.5 and 5.2).

		Without strong CYP3A inhibitors[3]	With strong CYP3A inhibitors[3]
Renal impairment[1]	Mild	50 mg	25 mg
	Moderate	50 mg	25 mg
	Severe	25 mg	Not recommended
Hepatic impairment[2]	Mild	50 mg	25 mg
	Moderate	25 mg	Not recommended

[1] Mild: GFR 60 to 89 ml/min/1.73 m^2; moderate: GFR 30 to 59 ml/min/1.73 m^2; severe: GFR 15 to 29 ml/min/1.73 m^2.
[2] Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
[3] Strong CYP3A inhibitors: itraconazole, ketoconazole, ritonavir, clarithromycin

Gender
No dose adjustment is necessary according to gender.

Paediatric population

The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No data are available.

Method of administration
The tablet is to be taken once daily, with liquids, swallowed whole and is not to be chewed, divided, or crushed. "

05 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

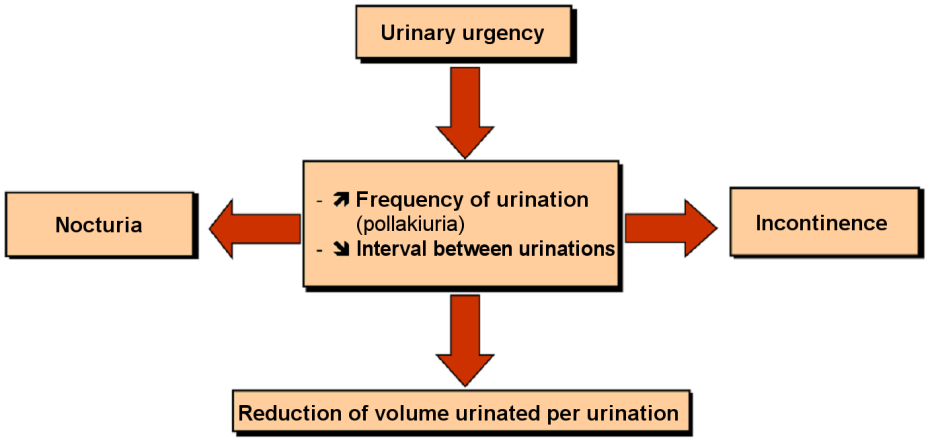
"Hypertension
BETMIGA has not been evaluated in severe uncontrolled hypertensive patients (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg); therefore it is not recommended for use in this patient population. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).

Patients with congenital or acquired QT prolongation
BETMIGA, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. "

06 THERAPEUTIC NEED

Overactive bladder is a clinical syndrome characterised by an irrepressible need to urinate (urgency) with or without incontinence, most often associated with increased micturition frequency and nocturia with no obvious urinary tract infection or local organic pathology likely to cause these symptoms.
Among the symptoms of overactive bladder, urgency is the pivotal symptom as it constitutes the trigger for any other associated symptoms (
Figure 1):

Figure 1 : Schematic diagram of overactive bladder syndrome (Chapple 2005)



The risk factors for overactive bladder notably include age, a history of one or more pregnancies, a history of vaginal birth and gynaecological-obstetrical traumas, a history of pelvic or abdominal surgery, obesity, intense physical activity and bed-wetting in childhood.

Several therapeutic options are available to treat urgency incontinence.[1,2]
Behavioural therapies (adjustment of fluid intake, reprogramming of voiding, keeping a voiding calendar) and perineal and sphincter rehabilitation are recommended (grade C). These different methods can be combined to achieve rehabilitation designed to inhibit bladder contractions. They can be offered as first-line treatment.
Behavioural therapies, perineal and sphincter rehabilitation and functional electrostimulation, surgery (sacral nerve stimulation (neuromodulation) in the event of resistance to drug therapy) and palliative treatments (incontinence pads, urine collection devices, urinary catheter, penile sheaths etc.) can also be considered as alternatives to drug therapies for urinary incontinence.

Anticholinergic therapy can also be offered first line or after the failure of behavioural therapy and/or rehabilitation (grade B). In a recent meta-analysis,[3] an improvement in urinary incontinence symptoms was observed when the anticholinergic drugs were combined with rehabilitation, compared with rehabilitation alone (RR of symptom improvement=0.55 95% CI [0.32; 0.93]).
Anticholinergic therapy is only prescribed:

- after diagnostic elimination of a urinary tract infection and urinary retention;
- if there are no contraindications to the use of anticholinergic drugs and if no treatment with an anticholinesterase is already under way.

Oxybutynin, tolterodine or trospium chloride are recommended (grade B). They have displayed moderate efficacy, but were significantly superior to a placebo in removing or relieving urgency incontinence (mean reduction of approximately one urinary incontinence episode every 48 hours). It is likely that tolterodine and trospium chloride are better tolerated than oxybutynin, but this likelihood is not supported by data that are sufficiently robust from a methodological point of view.

In view of the risk of urinary retention associated with anticholinergic drugs (oxybutynin, tolerodine and trospium chloride), monitoring the occurrence of a distended bladder, particularly in vulnerable elderly patients, is recommended. If anticholinergic therapy is considered, patients must be warned of the adverse effects (dry mouth, constipation, cognitive disorders), how long it takes to achieve maximum effectiveness (which may be up to 5 to 8 weeks) and the need to consultation a physician if no efficacy is observed after that

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1 Agence Nationale d'Accréditation et d'Evaluation en Santé Prise en charge de l'incontinence urinaire de la femme en medicine générale. Service des recommandations professionelles May 2003; 136 p.

2 Prof. François Haab (University of Paris VI, Tenon Hospital, Paris). Rapport sur le theme de l'incontinence urinaire remis à Mr Philippe Bas (Ministère de la Santé et des Solidarités). April 2007.

3 A.A. Alhasso et al. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Cochrane Review 2009.

period (particularly if it this concerns a "trial" anticholinergic drug prescribed without any prior urodynamic testing) or in the event of a urinary tract infection or difficulty in urinating.
These guidelines were issued prior to the Marketing Authorisations being granted for TOVIAZ (fesoterodine) and VESICARE (solifenacin), so they do not therefore cite fesoterodine and solifenacin as treatments for overactive bladder.

The Committee considered that the proprietary medicinal products VESICARE, CERIS and TOVIAZ constituted a therapeutic option in the management of increased micturition frequency and/or urgency and/or urgency incontinence in patients with overactive bladder.

The latest guidelines from Canada[4] and the USA[5] support the data in previous guidelines: all anticholinergic drugs have similar efficacy and immediate-release oxybutynin generates more adverse effects than the other anticholinergic drugs.
According to the authors of a recent meta-analysis,[6] the main disadvantage of anticholinergic drugs is their safety profile, dry mouth being the most commonly observed effect (in approximately 30% of patients receiving anticholinergic drugs). The most recent anticholinergic drugs (trospium, solifenacin, fesoterodine) have fewer adverse effects than their older counterparts (i.e. oxybutynin).

Worldwide, there are nine anticholinergic drugs in use (in an immediate- or prolonged-release form, administered orally or transdermally), but only three immediate-release drugs and one prolonged-release drug are available and reimbursed in France.
According to the authors of a meta-analysis,[7] prolonged-release formulations should be preferred over immediate-release formulations given their better safety profile (reduction in adverse effects).

According to the latest guidelines from the European Association of Urology,[8] there are no data to prove that one anticholinergic drug is superior to another in terms of improving the symptoms of urinary incontinence or quality of life; there are also no data to prove they are superior to behavioural therapy, but a combination of this therapy and anticholinergic drugs may be beneficial.
According to these recommendations, mirabegron (grade B) constitutes an alternative to anticholinergic drugs (grade A). Its long-term safety is not known.

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4 Traitements visant la vessie hyperactive : accent sur la pharmacothérapie. Directive clinique de la société des obstétriciens et gynécologiques du Canada. J Obstet Gynaecol Can 2012; 34:S1-S12

5 E.A. Gormley et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: American Urological Association Guideline. 2012.

6 C. Roxburgh et al. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. Cochrane Review 2009.

7 Novara G, Galfano A, Secco S et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008; 54:740-63. Epub 2008 Jul 9.

8 M.G. Lucas et al. Guidelines on urinary incontinence. European Association of Urology 2014.

07 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of therapeutic use and intended for the same population, as of the date of the assessment.

07.1 Medicinal products

INN	Same TC*	Name (Company)	Date of opinion	AB	IAB	Reimbursement
oxybutynin	No	DITROPAN (Sanofi Aventis)	26 June 2013 (reassessment of AB and IAB)	moderate	The TC cannot come to a decision	Yes
trospium	No	CERIS (Rottapharm)			IAB IV in terms of safety compared with DITROPAN	Yes
solifenacin	No	VESICARE (Astellas)				Yes
fesoterodine	No	TOVIAZ (Pfizer)				Not yet included on the list
tolterodine	No	DETRUSITOL (Pfizer)	-	-	-	No (marketed and not reimbursed)

*Therapeutic category

07.2 Other health technologies

The other health technologies are:
- behavioural therapies (adjustment of fluid intake, reprogramming of voiding, keeping a voiding calendar),
- Perineal and sphincter rehabilitation,
- surgery (sacral neuromodulation if resistance to drug therapy),

palliative treatments (incontinence pads, urine collection devices, etc.).

Conclusion
All the comparators listed are clinically relevant.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

BETMIGA has been granted a Marketing Authorisation in all countries of the European Union, in the USA (28 June 2012) and in Japan (1 July 2011).
Currently, the coverage of BETMIGA by National Health Insurance schemes is ensured in the UK (NICE has recommended BETMIGA as an alternative treatment for overactive bladder symptoms, but only for patients in whom anticholinergic drugs are contraindicated, ineffective or poorly tolerated), in Scotland and in Sweden (only in patients intolerant to anticholinergic drugs, as an alternative treatment with a safety profile differing from that of anticholinergic drugs).

09 ANALYSIS OF AVAILABLE DATA

The applicant has submitted the following in support of its application:

- three pivotal, phase III, randomised, double-blind, placebo-controlled studies, each lasting 12 weeks (SCORPIO, ARIES, CAPRICORN).

These three studies were the subject of a pooled analysis that had been planned beforehand.[9]

- the data from two studies performed in Japan: study 048 (not selected due to a data transferability problem) and study 051, a long-term open-label project (not selected by the Committee because it was not comparative and posed a transferability problem)
- the results of an open-label study to evaluate long-term safety (TAURUS)[10]
- the results of an indirect comparison (Mixed Treatment Comparison, MTC).

The three pivotal phase III studies evaluated the efficacy and safety of different dosages of mirabegron (25 mg, 50 mg and 100 mg) versus a placebo.
The dosage recommended in the SPC for mirabegron is 50 mg once daily.
The 25 mg dosage is used:
in cases of severe renal impairment if not combined with strong CYP3A inhibitors,
in cases of mild hepatic impairment if combined with strong CYP3A inhibitors,
in cases of moderate hepatic impairment if not combined with strong CYP3A inhibitors.
Since the patients included in the studies had neither hepatic impairment nor renal impairment, only the results corresponding to the SPC dosage (50 mg) will be presented.

9 Nitti V, Khullar V, van Kerrebroeck P, Herschorn S, Cambronero J, Angulo JC, Blauwet M, Dorrepaal C, Siddiqui E, Martin NE, Mirabegron for the treatment of overactive bladder : a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies, Int J Clin Pract 2013; 67: 619-32

10 Chapple C, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, Dorrepaal C, Martin N. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β3-adrenoceptor agonist, in overactive bladder. Eur Urol 2013; 63: 296-305.

09.1 Efficacy

	SCORPIO study (046)[11]	ARIES study (047)[12]	CAPRICORN study (074)[13]
Principal study objective	To evaluate the efficacy and safety of mirabegron (at doses of 50 mg and 100 mg) compared with a placebo in patients with symptoms of overactive bladder.		
Method	Phase III studies, randomised 1 : 1 : 1 : 1 in the SCORPIO study, 1 : 1 : 1 in the ARIES and CAPRICORN studies, double-blind, placebo-controlled. The SCORPIO study included an active-control group (tolterodine PR).		
Study duration:	12 weeks		
Inclusion criteria	– Age ≥ 18 years – Symptoms of overactive bladder for at least 3 months – Patients with a micturition frequency ≥8 times/24 h and at least three episodes of urinary urgency/24 h (grade 3 or 4 according to the PPIUS scale[14]) with or without incontinence during the 3 days prior to inclusion – Authorised concomitant treatments: alpha-blockers, 5α-reductase inhibitors, CYP3A4 inducers and loop diuretics if not initiated, modified or discontinued during the 30 days prior to the trial; programmes of behavioural rehabilitation or pelvic floor exercises authorised if initiated more than 30 days prior to starting the trial		
Treatment groups	– mirabegron 50 mg – mirabegron 100 mg – tolterodine PR 4 mg – placebo	– mirabegron 50 mg – mirabegron 100 mg – placebo	– mirabegron 25 mg – mirabegron 50 mg – placebo
Analysis population	– FAS population: all patients having taken at least one dose of treatment and having undergone at least one measurement of urinary parameters at inclusion and one post-inclusion – FAS-I population: subgroup of patients from the FAS population having notified at least one incontinence episode at inclusion – Safety analysis population: all patients having received at least one dose of treatment.		

[11] Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I et al. Efficacy and Tolerability of Mirabegron, a b3-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European–Australian Phase 3 Trial. Eur Urol 2013; 63: 283-95.

[12] Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized Phase III Trial of Mirabegron in Patients with Overactive Bladder. J Urol. 2013; 189:1388-95.

[13] Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, Stölzel M, Martin N, Gunther A, Van Kerrebroeck P, A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the 3-adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology early (2013): ttp://dx.doi.org/10.1016/j.urology.2013.02.077

[14] Notte SM, Marshall TS, Lee M, Hakimi Z, Odeyemi I, Chen WH, Revicki DA. Content validity and test-retest reliability of patient perception of intensity of urgency scale (PPIUS) for overactive bladder. Urology 2012; 12: 26.

To distinguish the physiological/normal need from the symptoms of urgency, the intensity of urgency episodes was assessed using the PPIUS scale from 0 to 4, urgency being defined by a grade 3 or 4 need to urinate.

Primary efficacy endpoint	Co-primary efficacy endpoints:[15] – change in the number of incontinence episodes/24 h after 12 weeks of treatment compared with the initial value (in the FAS-I population of patients incontinent at inclusion) – change in the number of micturitions/24 h after 12 weeks of treatment compared with the initial value (in the FAS population)
Secondary endpoints	- change in the volume urinated per micturition after 12 weeks compared with inclusion - change in the number of incontinence episodes/24 h after 4 weeks of treatment compared with inclusion - change in the number of micturitions/24 h after 4 weeks of treatment compared with inclusion These three endpoints underwent a hierarchical cluster analysis taking into account the multiplicity of the tests and therefore the risk of inflation of the alpha risk. They can therefore be used by the Committee. The following endpoints underwent exploratory analysis, and are not described. - change at weeks 8 and 12 compared with inclusion in the number of incontinence episodes/24 h and number of micturitions/24 h. - change at weeks 4, 8 and 12 compared with inclusion of the volume urinated per micturition. - change at weeks 4, 8 and 12 compared with inclusion of the number of urgency episodes (grade 3 or 4), the number of incontinence episodes, the intensity of urgency episodes, the number of episodes of nocturia and the number of incontinence pads used/24 h - percentage of responders based on incontinence episodes at weeks 4, 8 and 12 (reduction ≥50% in the number of incontinence episodes/24 h compared with inclusion) and percentage of responders at the final visit (no incontinence episodes) - Satisfaction with the treatment according to a VAS - Evaluation of quality of life using two questionnaires: Overactive Bladder Questionnaire (OAB-q), Patient perception of Bladder Condition (PPBC)
Calculation of the number of subjects required	This was based on two co-primary efficacy endpoints with similar hypotheses in the three studies: - evidence of a 0.7 reduction (standard deviation = 2.7) in the mean number of micturitions/24 h in each group treated with mirabegron compared with the placebo with a power of 90% - to analyse the mean number of incontinence episodes/24 h: based on a percentage of incontinent patients at inclusion of 65% in the SCORPIO and ARIES studies and 60% in the CAPRICORN study and a probability of 60.8% that a patient responds better on mirabegron than on the placebo in the SCORPIO and ARIES studies with a power of 97%.
Statistical analysis	The primary efficacy endpoints and the three secondary endpoints described above were tested according to a hierarchical sequential procedure (to guard against the risk of inflation of the alpha risk given the multiplicity of the tests) in the following order: 1. incontinence episodes/24 h (co-primary efficacy endpoint) 2. number of micturitions/24 h (co-primary efficacy endpoint) 3. volume urinated per micturition (secondary endpoint) 4. incontinence episodes after 4 weeks (secondary endpoint) 5. number of micturitions after 4 weeks (secondary endpoint). For each endpoint, the difference between mirabegron and the placebo needed to be statistically significant before moving to the following endpoint analysis. This adjustment procedure was not used for the other secondary endpoints. In the SCORPIO study, a comparison between mirabegron and tolterodine was not included in the protocol. Subgroup analyses (in particular in patients aged 65 years and over) were included in the pooled analysis protocol of the three pivotal studies. These analyses cannot be taken into account by the Committee given the absence of a method implemented to control the risk of inflation of the alpha risk due to the multiple comparisons.

[15] Evaluation of the different efficacy parameters was performed from data collected by the patients themselves in a urination diary which was to be completed for the 3 consecutive days prior to each consultation scheduled in the study.

Characteristics of the patients included:

In all the studies, the characteristics of the patients included in the different treatment groups were comparable.
The patients were aged on average 58 to 60 years in the three studies and in all the treatment groups. There were usually more women (almost 70%) and the majority of patients had already received treatment for their overactive bladder (52 to 53% depending on the groups). This treatment had usually been discontinued due to inefficacy (66-67%). The initial number of incontinence episodes per 24 h in the FAS-I population was between 2.4 to 3 depending on the studies and the treated groups, and the number of urgency episodes/24 h was between 2.2 and 2.5. The mean number of micturitions/24 h was close to 12 and the number of urgency episodes was between 5.4 and 5.9, depending on the studies and the treatment groups *(see Tables 1 and 2).*

Table 1: Principal characteristics of the included patients (FAS population)

Studies	SCORPIO			ARIES		CAPRICORN		Pooled analysis	
Treatment group	**Mirabegron 50 mg N=473**	**Tolterodine PR 4 mg N=475**	**Placebo n=480**	**Mirabegron 50 mg N=425**	**Placebo n=433**	**Mirabegron 50 mg N=426**	**Placebo n=415**	**Mirabegron 50 mg N=1324**	**Placebo n=1328**
Mean age (years) (SD standard deviation)	59.2 (12.1)	59.1 (12.7)	59.3 (12.1)	59.6 (13.3)	60.1 (13.7)	60.4 (12.3)	58.2 (13.8)	59.7 (12.6)	59.2 (13.2)
≥ 65 years	171 (36.2%)	184 (38.7%)	178 (37.1%)	164 (38.6%)	172 (39.7%)	164 (38.5%)	154 (37.1%)	499 (37.7%)	504 (38.0%)
≥ 75 years	43 (9.1%)	33 (6.9%)	43 (9.0%)	58 (13.6%)	67 (15.5%)	48 (11.3%)	44 (10.6%)	149 (11.3%)	154 (11.6%)
Previous OAB treatment	240 (50.7%)	231 (48.6%)	238 (49.6%)	242 (56.9%)	249 (57.5%)	206 (48.4%)	217 (52.3%)	688 (52.0)	704 (53.0)
Discontinued previous treatment due to:									
Insufficient efficacy	160 (66.7%)	155 (67.1%)	159 (66.8%)	161 (66.5%)	166 (66.7%)	143 (69.4%)	141 (65.0%)	46 (67.4)	466 (66.2)
Poor tolerance	65 (27.1%)	56 (24.2%)	68 (28.6%)	49 (20.2%)	60 (24.1%)	59 (28.6%)	57 (26.3%)	173 (25.1)	185 (26.3)

Table 2: Characteristics of overactive bladder (FAS and FAS-I populations)

Studies	SCORPIO			ARIES		CAPRICORN		Pooled analysis	
Treatment groups	**Mirabegron 50 mg**	**Tolterodine PR 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**
FAS-I population, N	293	300	291	312	325	257	262	862	878
Number of incontinence episodes /24 h	2.83 (2.83)	2.63 (2.56)	2.67 (2.40)	2.77 (2.65)	3.03 (3.08)	2.51 (2.35)	2.43 (2.35)	2.7 (2.63)	2.7 (2.7)
Number of urgency episodes /24 h	2.46 (2.60)	2.28 (2.28)	2.36 (2.18)	2.30 (2.36)	2.51 (2.46)	2.27 (2.22)	2.19 (2.20)	2.42 (0.08)	2.42 (0.08)
FAS population, N	473	475	480	425	433	426	415	1324	1328
Number of micturitions /24 h	11.65 (2.97)	11.55 (2.78)	11.71 (3.14)	11.80 3.46)	11.51 (3.27)	11.66 (3.22)	11.48 (2.90)	11.7 (3.21)	11.6 (3.11)
Number of urgency episodes /24 h	5.69 (3.65)	5.77 (3.45)	5.76 (4.00)	5.88 (3.84)	5.61 (3.24)	5.80 (3.57)	5.40 (3.31)	5.8 (0.10)	5.61 (0.10)
Number of episodes of nocturia/24 h	1.87 (1.29)	1.95 (1.41)	1.98 (1.41)	1.90 (1.61)	1.93 (1.63)	2.03 (1.54)	1.78 (1.27)	2.22* (0.04)	2.18** (0.04)

**number of patients=1148, **number of patients=1156*

Efficacy result for the primary efficacy endpoint:

A statistically significant reduction in the number of incontinence episodes and the number of micturitions per 24 h compared with the placebo was observed in the mirabegron 50 mg groups in each of the three studies and in the pooled analysis.

No difference was observed in the SCORPIO study between the tolterodine PR 4 mg and placebo groups *(see Table 3).*

Table 3: Results concerning the co-primary efficacy endpoints: reduction at the final visit compared with inclusion of the number of incontinence episodes /24 h (FAS-I population) and the number of micturitions/24 h (FAS population)

Studies	SCORPIO			ARIES		CAPRICORN		Pooled analysis	
Treatment groups	**Mirabegron 50 mg**	**Tolterodine PR 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**
Number of incontinence episodes /24 h									
FAS-I population, N	293	300	291	312	325	257	262	862	878
Value at inclusion	2.83 (0.16)	2.63 (0.15)	2.67 (0.14)	2.77 (0.15)	3.03 (0.17)	2.51 (0.15)	2.43 (0.14)	2.71 (0.09)	2.73 (0.09)
Final visit	1.22 (0.13)	1.42 (0.14)	1.54 (0.14)	1.33 (0.13)	1.81 (0.15)	1.13 (0.13)	1.54 (0.15)	1.23 (0.08)	1.64 (0.09)
Change (adjusted mean)	-1.57 (0.11)	-1.27 (0.11)	-1.17 (0.11)	-1.47 (0.11)	-1.13 (0.11)	-1.38 (0.12)	-0.96 (0.12)	-1.49 (0.07)	-1.10 (0.07)
Difference vs. placebo (adjusted mean, 95% CI)	-0.41 [-0.72; -0.09]	-0.10 [-0.42; 0.21]		-0.34 [-0.66; -0.03]		-0.42 [-0.76; -0.08]		-0.40 [-0.58; -0.21]	
p	0.003	NS		0.03		0.001		< 0.001	
Number of micturitions /24 h									
FAS population	473	475	480	425	433	426	415	1324	1328
Value at inclusion	11.65 (0.14)	11.55 (0.13)	11.71 (0.14)	11.80 (0.17)	11.51 (0.16)	11.66 (0.16)	11.48 (0.14)	11.70 (0.09)	11.58 (0.08)
Final visit	9.70 (0.14)	9.97 (0.16)	10.35 (0.14)	10.09 (0.17)	10.51 (0.16)	10.04 (0.17)	10.33 (0.17)	9.93 (0.09)	10.39 (0.09)
Change (adjusted mean)	-1.93 (0.11)	-1.59 (0.11)	-1.34 (0.11)	-1.66 (0.13)	-1.05 (0.13)	-1.60 (0.125)	-1.18 (0.12)	-1.75 (0.07)	-1.20 (0.071)
Difference vs. placebo (adjusted mean, 95% CI)	-0.60 (0.16) [-0.90; -0.29]	-0.25 (0.16) [-0.55; 0.06]		-0.61 (0.19) [-0.98; -0.24]		-0.42 (0.17) [-0.76; -0.08]		-0.55 (0.10) [-0.75; -0.36]	
p	< 0.001	NS		0.001		0.015		< 0.001	

Secondary endpoints:

SCORPIO study:

Change in the volume urinated per micturition at the final visit compared with inclusion FAS population			
Treatment groups	Mirabegron 50 mg N=472	Tolterodine PR 4 mg N=475	Placebo n=480
Change/inclusion (adjusted mean)	24.2 (2.01)	25.0 (2.00)	12.3 (1.99)
Mean difference versus placebo 95% CI	11.9 (2.83) [6.3; 17.4]	12.6 (2.83) [7.1; 18.2]	
p values	< 0.001	< 0.001	
Change in the number of incontinence episodes /24 h at week 4 compared with inclusion FAS-I population,			
Treatment groups	Mirabegron 50 mg N=293	Tolterodine PR 4 mg N=299	Placebo n=291
Change/inclusion (adjusted mean)	-1.04 (0.118)	-1.00 (0.117)	-0.65 (0.118)
Mean difference versus placebo 95% CI	-0.39 (0.167) [-0.71; -0.06]	-0.35 (0.166) [-0.68; -0.03]	
p values	0.002	0.019	
Change in the number of micturitions /24 h at week 4 compared with inclusion FAS population			
Treatment groups	Mirabegron 50 mg N=471	Tolterodine PR 4 mg N=474	Placebo n=480
Change/inclusion (adjusted mean)	-1.16 (0.097)	-1.10 (0.096)	-0.77 (0.096)
Mean difference versus placebo 95% CI	-0.40 (0.136) [-0.66; -0.13]	-0.33 (0.136) [-0.60; -0.06]	
p values	0.004	0.016	

ARIES study:

Change in the volume urinated per micturitions at the final visit compared with inclusion FAS population		
Treatment groups	Mirabegron 50 mg N=425	Placebo n=433
Change/inclusion (adjusted mean)	18.2 (2.44)	7.0 (2.41)
Mean difference versus placebo 95% CI	11.1 (3.43) [4.4; 17.9]	
p value	0.001	
Change in the number of incontinence episodes 24 h at week 4 compared with inclusion FAS-I population		
Treatment groups	Mirabegron 50 mg N=3129	Placebo n=325
Change/inclusion (adjusted mean)	-1.20 (0.119)	-0.72 (0.116)
Mean difference versus placebo 95% CI	-0.48 (0.166) [-0.80; -0.15]	
p value	0.003	
Change in the number of micturitions /24 h at week 4 compared with inclusion FAS population		
Treatment groups	Mirabegron 50 mg N=425	Placebo n=433
Change/inclusion (adjusted mean)	-1.19 (0.129)	-0.77 (0.127)
Mean difference versus placebo 95% CI	-0.42 (0.182) [-0.77; -0.06]	
p value	0.022	

CAPRICORN study:

Change in the volume urinated per micturitions at the final visit compared with inclusion FAS population		
Treatment groups	Mirabegron 50 mg N=426	Placebo n=415
Change/inclusion (adjusted mean)	20.7 (2.20)	8.3 (2.23)
Mean difference versus placebo 95% CI	12.4 (3.13) (6.3; 18.6)	
p value	< 0.001	
Change in the number of incontinence episodes /24 h at week 4 compared with inclusion FAS-I population,		
Treatment groups	Mirabegron 50 mg N=255	Placebo n=262
Change/inclusion (adjusted mean)	-1.13 (0.122)	-0.62 (0.120)
Mean difference versus placebo 95% CI	-0.51 (0.171) (-0.85; -0.17)	
p value	<0.001	
Change in the number of micturitions /24 h at week 4 compared with inclusion FAS population		
Treatment groups	Mirabegron 50 mg N=424	Placebo N=415
Change/inclusion (adjusted mean)	-1.14 (0.122)	-0.78 (0.124)
Mean difference versus placebo 95% CI	-0.37 (0.174) (-0.71; -0.03)	
p value	0.035	

A statistically significant increase in the volume urinated per micturition after 12 weeks of treatment, and a statistically significant reduction in the numbers of incontinence episodes/24 h and the number of micturitions/24 h after 4 weeks of treatment were observed by comparison with inclusion in each of the three studies in the group treated with mirabegron 50 mg compared with the placebo.

09.2 Safety/Adverse effects

9.2.1 Study data

The most commonly reported adverse events with mirabegron at a dosage of 50 mg/day (reported by more than 3% of patients in the pooled analysis) were: hypertension[16] (7.5% of patients, 103/1375), nasopharyngitis (3.9% of patients, 54/1375) and urinary tract infection (2.9% of patients, 40/1375). Hypertension affected 7.6% of patients on placebo (105/1380), nasopharyngitis affected 2.5% of patients (32/1380) and urinary tract infection 1.8% of patients (25/1380).

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Event defined a priori in all the phase III protocols, corresponding to any patient meeting ≥1 of the following criteria: mean systolic blood pressure (SBP) ≥140 mmHg and/or mean diastolic blood pressure (DBP) ≥90 mmHg during two successive evaluations under treatment in a patient who was not hypertensive at baseline, *or* increase in mean SBP ≥20 mmHg and/or increase in mean DBP ≥10 mmHg during two successive evaluations under treatment in a patient who was hypertensive at baseline, *or* initiation or increase in dosage of antihypertensive medication during the study, *or* decision by the investigator based on the clinical examination.

Treatment discontinuations ranged from 9% to 15% depending on the studies and the treatment groups. In total, they concerned (result from the pooled analysis) 12.1% of patients treated with mirabegron 50 mg (166/1375) and 12.7% of patients on the placebo (175/1380). In around 4% of patients in each group, this discontinuation was due to an adverse event.
The most common treatment-related adverse events that resulted in treatment discontinuation were: headaches (mirabegron: 5/2736 (0.2%); placebo: 4/1380 (0.3%); tolterodine: 2/495 (0.4%)) and hypertension (mirabegron: 5/2736 (0.2%); placebo: 2/1380 (0.1%); tolterodine: 1/495 (0.2%)).
The total incidence of serious treatment-related adverse events that resulted in treatment discontinuation were comparable with the three doses of mirabegron (no dose-dependent effect).
Most of the adverse events were of mild to moderate severity.

The TAURUS study[17,18], which was randomised 1 : 1 : 1, double-blind, versus tolterodine PR 4 mg, evaluated the long-term safety (52 weeks) of mirabegron (administered at doses of 50 mg/day and 100 mg/day) in 2444 patients (820 in the mirabegron 50 mg group, 820 in the mirabegron 100 mg group, 812 in the tolterodine group, included according to the same criteria as the three pivotal studies).
Adverse events were observed in 59.7% of the patients in the mirabegron 50 mg group (485/812) and 62.6% of the patients in the tolterodine PR 4 mg group (508/812). These events led to treatment discontinuation in 5.9% of the patients on mirabegron and 5.7% of the patients on tolterodine.
The most commonly reported adverse events (≥ 2% of patients) were:

- arterial hypertension (6% of patients on mirabegron versus 5% on tolterodine),
- dry mouth (2% of patients on mirabegron versus 8% on tolterodine),
- constipation (2% of patients on mirabegron versus 2% on tolterodine),
- headaches (2% of patients on mirabegron versus 2% on tolterodine).

They were all mild or moderate.
These events were related to the treatment in 26.2% of the patients on mirabegron 50 mg and 27.6% of the patients on tolterodine. These events led to treatment discontinuation in 4.3% of the patients on mirabegron and 3.8% of the patients on tolterodine.

9.2.2 SPC data

"The safety of mirabegron was evaluated in 8433 patients with OAB, of whom 5648 received at least one dose of mirabegron in the phase II/III clinical programme, and 622 patients received mirabegron for at least 1 year (365 days). In the three 12-week, phase III, double-blind, placebo-controlled studies, 88% of the patients completed treatment with mirabegron, and 4% of patients discontinued treatment due to adverse events. Most of the adverse events were mild to moderate in severity.

The most common adverse events reported in patients treated with mirabegron 50 mg during the three 12-week, phase III, double-blind, placebo-controlled studies were tachycardia and urinary tract infections. The incidence of tachycardia was 1.2% in patients receiving mirabegron 50 mg. Tachycardia led to treatment discontinuation in 0.1% of patients receiving mirabegron 50 mg. The incidence of urinary tract infections was 2.9% in patients receiving mirabegron 50 mg, but none of these infections led to treatment

17 Chapple C, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, Dorrepaal C, Martin N. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a -adrenoceptor agonist, in overactive bladder. Eur Urol 2013; 63: 296-305.

18 A Randomized, Double-Blind, Parallel Group, Active Controlled, Multi center Long-term Study to Assess the Safety and Efficacy of the Beta-3 Agonist Mirabegron (YM178) 50 mg qd and 100 mg qd in Subjects With Symptoms of Overactive Bladder. Clinical Study Report. 8 December 2010.

discontinuation in any of the patients receiving mirabegron 50 mg. Serious adverse events included one case of atrial fibrillation (0.2%)

The adverse events observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week, phase III, double-blind, placebo-controlled studies. "

9.2.3 The Risk Management Plan (RMP)

The RMP provides for:

- monitoring for the following identified significant risks: increased heart rate, tachycardia and hypersensitivity reactions,
- monitoring for the following potential significant risks: QT interval prolongation, increased blood pressure, urinary tract infection, urine retention, embryonic-foetal toxicity and concomitant administration with medicinal products with a narrow therapeutic range or whose doses are individually titrated and which are metabolised by CYP2D6,
- implementation of a cohort study conducted in elderly patients aged 65 years and over, at high cardiovascular risk, with overactive bladder and treated with anticholinergic drugs or mirabegron.

09.3 Other data: indirect comparison (MTC)

In the absence of data on direct comparisons other than the comparison with tolterodine in a form which is not marketed in France during the SCORPIO study, a systematic review of the literature review was made in order to perform an indirect comparison of the efficacy and safety of mirabegron versus other treatments for overactive bladder; i.e. anticholinergic drugs *(data not published).*

The protocol used to analysis the indirect comparisons was as follows:

- inclusion of all comparative studies lasting 8 to 16 weeks for the efficacy analysis and 4 to 16 weeks for the safety analysis, published between 2000 and 2012 (with searches of MEDLINE and Embase and the Cochrane Central Register of Controlled Trials)
- studies that included adult patients with overactive bladder,
- studies that evaluated the following treatments: oxybutynin, trospium chloride (used at a dosage of 60 mg, not recommended in France), tolterodine, solifenacin, fesoterodine, mirabegron:[19]

The criteria used to evaluate efficacy were derived from the co-primary endpoints chosen for the pivotal studies of mirabegron, namely micturition frequency, incontinence and urgency incontinence.

To guarantee a comparable representativeness of the patients, the selection of publications did not include publications prior to 2000, out of concern for consistency in the population studied because the definition of overactive bladder was only formalised after 2001.
Whenever possible, a meta-analysis was performed, providing an estimation of the degree of effect regarding the progression of symptoms between inclusion and end of treatment, using fixed effects models and random effects models.

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19 The anticholinergic treatments identified in the publications corresponded to immediate-release and prolonged-release dosage forms (the latter are not available in France for tolterodine, trospium and oxybutynin). The two formulations of a same active ingredient were assumed to have similar efficacy, and were therefore not separated for efficacy analyses. However, the different formulations of a same treatment were separated for safety analyses since the dosage forms were likely to affect the safety profile.

Analysis was limited to a dosage of 50 mg for mirabegron.

Results
The literature search identified 1934 references, and 127 publications describing 46 studies were initially selected.
The MTC analysis finally involved 40 studies which included 26,033 patients.

Regarding the efficacy endpoints:

- *for the number of micturitions/24 h* (analysed in 23 studies), there was no difference between mirabegron and the anticholinergic drugs, apart from a difference in favour of mirabegron compared with tolterodine 4 mg and a difference in favour of solifenacin 10 mg compared with mirabegron.
- *for the number of incontinence episodes/24 h* (analysis of 15 studies), no difference was observed between mirabegron and the anticholinergic drugs, apart from a difference in favour of solifenacin 5 and 10 mg compared with mirabegron.
- *for the number of urgency episodes/24 h* (analysed in 17 studies), there was no difference between mirabegron and the anticholinergic drugs. However, a difference in favour of solifenacin 10 mg compared with mirabegron was revealed.

The following adverse events (amongst the most common effects of anticholinergic drugs) were evaluated: dry mouth, constipation, blurred vision.

Regarding the risk of occurrence:
dry mouth (analysis of 40 studies): there was no difference between mirabegron and the placebo, and mirabegron was better tolerated than all the anticholinergic drugs.
constipation (analysis of 37 studies): there was no difference between mirabegron and the placebo and the anticholinergic drugs, apart from fesoterodine 8 mg and solifenacin 5 mg and 10 mg in comparison with which mirabegron had a better safety profile.
As for blurred vision (analysis of 23 studies), no difference was revealed between the treatments.

Remarks:

- in this indirect comparison, all the available alternatives were taken into consideration;[20]
- a systematic but non-exhaustive search was performed;
- there were differences between the studies selected for the indirect comparison in terms of duration of treatment, primary efficacy endpoint, and previous treatments;
- The exchangeability assumption was not discussed (the interaction factors were not assessed), nor was the comparability of the studies in terms of the degree of effect;
- the Bayesian method of analysis used was partially validated at the statistical level (the a *prioris* were not informative, and the independence of the results compared with the a prioris was not verified).

20 However, trospium chloride was administered at a clearly higher dose than that recommended in France, which is 40 mg/day.

010 SUMMARY AND DISCUSSION

The efficacy of mirabegron was evaluated in the treatment of overactive bladder characterised by symptoms of urgency and increased micturition frequency with or without urinary incontinence in three randomised, double-blind, placebo-controlled studies, each with a duration of 12 weeks.
These studies were the subject of a pooled analysis that had been pre-specified in the study protocols.
They evaluated different dosages of mirabegron (25 mg, 50 mg and 100 mg). The dosage recommended by the SPC is 50 mg once daily, so only the results involving this dose are described here.
One study included an active-treatment group (tolterodine PR 4 mg, not reimbursed in France) but the protocol did not provide for a comparison with mirabegron.
Hierarchical cluster analysis of the two co-primary efficacy endpoints and three secondary endpoints (limited clinical relevance because of an evaluation at 4 weeks of treatment) was included in the protocol in order to control the risk of inflation of the alpha risk due to the multiple comparisons.

In all the studies, the characteristics of the patients included in the different mirabegron 50 mg treatment groups were comparable. The mean age of patients was 58 to 60 years and the majority had already received anticholinergic therapy for their overactive bladder (52 to 53%, depending on the groups). This treatment had most often been discontinued due to inefficacy in 66 to 67% of patients.
The initial number of incontinence episodes per 24 h in the sub-population who were incontinent at inclusion, ranged from 2.4 to 3 depending on the studies and the treated groups, the number of urgency incontinence episodes/24 h was between 2.2 and 5.9 and the number of urgency episodes was 5.4 to 5.9, depending on the studies. The mean number of micturitions/24 h was close to 12 (as in the studies which evaluated the anticholinergic drugs).

The co-primary efficacy endpoints were the change in the mean number of incontinence episodes/24 h and the change in the mean number of micturitions/24 h between the start and the end of treatment. In the pooled analysis:

- the reduction in the number of incontinence episodes/24 h was 1.49 episodes in the mirabegron 50 mg/day group and 1.10 in the placebo group (difference compared with the placebo of -0.40 95% CI [-0.58; -0.21] p<0.001)

- the reduction in the number of micturitions/24 h was 1.75 in the mirabegron 50 mg/day group and 1.20 in the placebo group (difference compared with the placebo of -0.55 95% CI [-0.75; 0.36] p<0.001)

Similar results were obtained in the three studies.

Concerning safety, the main adverse events reported in the three pivotal studies (N=2755 patients) were hypertension, rhinopharyngitis and urinary tract infection. Treatment discontinuation rates ranged from 9% to 15%, depending on the studies and the treatment groups.
In the TAURUS study on long-term safety (52 weeks) which evaluated 2444 patients, 812 of whom were treated with mirabegron 50 mg, the main adverse events were arterial hypertension, constipation and headaches and resulted in treatment discontinuations in around 6% of patients on mirabegron.
The adverse events were of mild to moderate intensity.

Comments
The aetiological factors which cause overactive bladder syndrome are unknown. No urodynamic assessment was performed prior to treatment initiation, although such a procedure is particularly

advised in the event of first-line treatment failure. It is difficult to draw any conclusions as regards the representativeness of the studied cohorts in comparison to general urology practice.
The inclusion of a majority of patients who had already been treated with anticholinergic drugs and especially in whom treatment had failed (66%) is a possible bias. A comparison versus anticholinergic drugs in treatment-naive patient groups would have been more relevant.
It should be noted, as has already been the case during studies performed with anticholinergic drugs in overactive bladder,[21] that the placebo effect was significant.
The reduction in the number of incontinence episodes/24 h was evaluated in a sub-population of patients. Despite the statistical measures taken (hierarchical cluster analysis), an overestimation of the effect cannot be excluded.
As a reminder, the difference observed versus the placebo in terms of reducing micturition frequency (efficacy endpoint common to the evaluation of anticholinergic drugs and mirabegron) was 1 micturition/24 h on anticholinergic treatment (in patients with the same characteristics as those on mirabegron with 12 micturitions at inclusion). The benefit of treatment with mirabegron (difference of 0.55 micturitions/24 h compared with the placebo) was therefore small.

It is regrettable:
- that quality of life (whose improvement is one of the objectives of symptomatic treatments) and the percentage of patients responding to treatment were only analysed in an exploratory manner;
- that the protocol did not include a comparison between the two active treatments (mirabegron and tolterodine);
- that the 25 mg dosage of mirabegron was not evaluated (the studies did not include patients with hepatic or renal impairment for whom this low dose is intended);
- that there were no data versus an active comparator, particularly in treatment-naive patients.

The following should be noted:
- as with anticholinergic drugs, the short duration of evaluation of mirabegron during the studies (12 weeks);
- a lack of data in elderly subjects;
- as with anticholinergic drugs, a lack of evaluation of the change in urgency episodes, as a primary efficacy endpoint in the studies, despite the fact that this is a cardinal symptom of overactive bladder.

The Committee does not have any data directly comparing mirabegron with another drug therapy that is currently reimbursed. None of them can be recommended in preference over another. The Committee regrets the lack of comparison with other therapeutic methods, in particular behavioural therapies.

The Committee also has results of an indirect comparison between mirabegron and all the anticholinergic drugs with the same therapeutic indication (oxybutynin, trospium, tolterodine, solifenacin, fesoterodine). In view of certain methodological limitations (see section 09.3), the results of this indirect comparison needs to be interpreted with caution.
There was no difference between the treatments in terms of efficacy apart from an observed difference in favour of solifenacin compared with mirabegron for the three efficacy endpoints (number of micturitions/24 h, number of incontinence episodes/24 h, number of urgency episodes/24 h).
Only one study with good methodological quality would enable this result to be confirmed or invalidated. The registration authorities have requested a study versus solifenacin to be carried out in patients in whom the other anticholinergic drugs were not effective.

21 Lee S, Malholtra B, Creanga D, Carlsson M, Glue P. A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder. BMC Med Res Methodol 2009;9:55.

The lack of difference in relation to the other anticholinergic drugs does not support a conclusion of a difference regarding comparative efficacy and no ranking of the treatments is possible.
Concerning safety, no difference between the treatments was observed apart from the characteristic anti-muscarinic events seen with anticholinergic drugs (dry mouth, constipation) regarding which mirabegron appears to have a better safety profile.
For the Scottish assessment agency, the data from this indirect comparison suggested a lack of difference between mirabegron 50 mg and anticholinergic drugs in terms of efficacy, apart from efficacy which appeared to be reduced by comparison with solifenacin with respect to theurgency incontinence and number of micturitions endpoints. An overestimation of the effect of mirabegron cannot be excluded in light of the methodological biases. These results must therefore be interpreted with caution.
Despite this indirect comparison having several limitations, we do not know if mirabegron is equivalent or superior to anticholinergic drugs. A direct comparative study with an anticholinergic drug would have been useful especially since a study versus trospium chloride (CERIS) would have been possible in light of the dates of their development.

011 PLANNED STUDIES

Currently ongoing studies include the BEYOND study, which is a phase IIIb, randomised, double-blind study that aims to evaluate the efficacy and safety of mirabegron versus solifenacin (VESICARE) in patients with overactive bladder who are dissatisfied with the efficacy of an anticholinergic medication other than solifenacin. The results are expected in 2014.

012 THE MEDICINE'S THERAPEUTIC USE

Extrapolation of the results of the clinical studies available into clinical practice raises questions as to the role of this medicinal product in therapeutic strategy.
A comparative study between BETMIGA and an anticholinergic in treatment-naive patients only would enable clarification regarding whether mirabegron is equivalent or superior to anticholinergic drugs as first-line treatment.
The indirect comparison data are not sufficient to rank the treatments.
Therefore, the role of BETMIGA in therapeutic strategy is difficult to specify in light of the characteristics of the included patients (in particular previous and concomitant treatments with an anticholinergic drug) and the absence of studies versus anticholinergic drugs. It is left to the discretion of prescribing physicians.

013 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

013.1 Actual benefit

◗ Urge incontinence is characterised by the involuntary loss of urine preceded by an urgent and
◗ Urgency incontinence is characterised by the involuntary loss of urine preceded by an urgent and irrepressible need to urinate resulting in micturition that cannot be delayed.

Overactive bladder is a condition that causes a marked deterioration in quality of life and possible development of a social handicap.

- BETMIGA is intended as symptomatic therapy.
- Its efficacy was superior to placebo but the degree of effect was low (in particular a reduction of around one half of a daily micturition compared with the placebo). Not being an anticholinergic, mirabegron is free of antimuscarinic effects but there are doubts concerning its long-term safety, notably of a cardiovascular type. Therefore, the efficacy/safety ratio for this medicinal product is low.
- The role of BETMIGA in therapeutic strategy is difficult to specify in light of the available data. Alternative treatments are available. Anticholinergic drug therapy can be offered as first-line therapy or after the failure of behavioural and/or rehabilitation therapy.

- *Public health benefit:*

  The public health burden of urgency,, urgency incontinence and increased micturition frequency in adult patients with overactive bladder is low.

  The symptomatic management of urgency,, urgency incontinence and/or increased micturition frequency in these patients does not constitute a public health need.

  Given the available data, the proprietary medicinal product BETMIGA has not shown any impact in terms of reducing morbidity or improving quality of life. The transferability of the data into clinical practice is not guaranteed given the included population.

  As a result, in the current state of knowledge and in view of the fact that therapies are already available, the proprietary medicinal product BETMIGA does not offer any public health benefit.

Taking account of these points, the Committee considers that the actual benefit of BETMIGA is low in the symptomatic treatment of urgency and increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome.
This actual benefit is provisional pending the results of the study versus VESICARE.

013.2 Improvement in actual benefit (IAB)

Taking into account:

- the low observed efficacy versus placebo, particularly in terms of reducing daily micturition frequency,
- the limitations affecting evaluation (exploratory quality of life data, absence of evaluation *versus* anticholinergic drugs in treatment-naive patients, absence of direct comparisons versus therapeutic alternatives),
- the available data, and in particular the indirect comparison which does not enable BETMIGA to be distinguished from anticholinergic drugs nor enable treatments to be prioritised relative to one other,

no conclusion regarding comparative efficacy can be formulated and the therapeutic advance procured by BETMIGA is difficult to assess when compared with existing alternative medicinal products (anticholinergic drugs) with the same indication.
The Committee therefore considers that BETMIGA does not procure an improvement in actual benefit (LAB level V, non-existent) in the symptomatic treatment of urgency and increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder syndrome and, in particular, pending the results of the study versus VESICARE.

014 TARGET POPULATION

The target population corresponds to all adult patients with an overactive bladder.

According to a European study[22] (Germany, France, United Kingdom, Italy, Sweden, Spain), the mean prevalence of overactive bladder is 16.6% in the population aged over 40 years. In France, the prevalence in this population[23] is 12%, i.e. about 3.9 million people are affected.
The proportion of patients consulting doctors for this reason is 60%, i.e. about 2.4 million patients.
Of these, at the time of the European cross-sectional survey which is the only relevant data available in literature, only 27% were on medication.
Applying these results to the French population, the population likely to be treated with a medicinal product for overactive bladder is around 640,000 patients.

Overall, the target population of BETMIGA is about 640,000 patients.

015 COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

Proposed reimbursement rate: 15%

Packaging
Appropriate for the prescribing conditions.

Request for data
The Committee will re-assess its conclusions in light of new data, in particular comparative data versus anticholinergic drugs (a study is ongoing in patients in whom an anticholinergic drug other than VESICARE was ineffective).

[22] Milsom et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; 87: 760-766.
[23] Population aged 40 years and over on 1st January 2012: 32,920,200. INSEE age pyramid 2012.