

Impact of mirabegron extended-release on the treatment of overactive bladder with urge urinary incontinence, urgency, and frequency

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Abstract: Overactive bladder is a highly prevalent disorder with a significant impact on quality of life. Antimuscarinic agents are commonly used, but persistence is limited due to unsatisfactory efficacy and/or tolerability. Mirabegron is the first beta-3 adrenoceptor agonist approved for the treatment of overactive bladder syndrome. This paper reviews the pharmacology, mechanism of action, efficacy, and safety of mirabegron. A PubMed search of all English articles pertaining to mirabegron was performed. An alternative to antimuscarinics, mirabegron has a unique mechanism, improves overactive bladder symptoms and quality of life, and has limited adverse effects and few contraindications.

Keywords: overactive bladder, incontinence, beta-3 agonist, mirabegron

Introduction

Overactive bladder (OAB) syndrome consisting of urgency, with or without urge incontinence, often with frequency and nocturia, is a highly prevalent disorder with a significant impact on quality of life. It is estimated that approximately 11%–15% of adults worldwide have OAB symptoms.^{1,2} The prevalence of OAB increases with age, affecting 30%–40% of the population >75 years of age.^{2,3} It is estimated that 546 million individuals worldwide will be affected by OAB by 2018.⁴

OAB symptoms are the result of storage phase dysfunction. The etiology of OAB may be multifactorial, but at least two afferent signaling pathways have been defined,⁵ ie, the myogenic and urothelial pathways.^{6,7} First-line treatment for OAB is behavioral therapy.⁸ Until recently, the only approved pharmacologic treatment for the management of OAB symptoms was antimuscarinic therapy. There are a variety of antimuscarinic agents available, which vary in their method of delivery, dose flexibility, molecular structure, muscarinic receptor affinity, and side effect profile. However, as a group, these agents are recognized to be safe and effective in the management of OAB symptoms.^{9–11} Compliance with antimuscarinic therapy is limited, and efficacy, tolerability, and cost have been cited as contributors.^{12,13} Mirabegron, the first beta-3 adrenoceptor agonist approved for the treatment of OAB symptoms, provides an alternative to antimuscarinic therapy and has a unique mechanism of action and side effect profile. This paper reviews the pharmacology, mechanism of action, efficacy, and safety of mirabegron based on a PubMed search of all English articles on mirabegron.

Compound and mechanism of action

The chemical name for mirabegron is (R)-(2-(2-amino-1,3-thiazol-4-yl)-N-(4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl)phenyl)acetamide. Mirabegron is a potent and selective agonist for the human beta-3 adrenoceptor. A radioligand competition binding

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assay with mirabegron found a 1,000-fold higher affinity for the human beta-3 adrenoceptor over the human beta-1 adrenoceptor and beta-2 adrenoceptor. Mirabegron facilitates bladder filling and extends the storage phase by activating the beta-3 adrenoceptor.¹⁴ In mammals, detrusor relaxation is primarily mediated by the cyclic adenosine monophosphate pathway, which is activated by binding of noradrenalin to the beta adrenoceptor.^{11,15} Both animal and human bladders have beta-1, beta-2, and beta-3 adrenoceptors.¹¹ In the human bladder, the beta-3 is the more common type of adrenoceptor, and appears to be the main one mediating human detrusor relaxation.^{16–18} Animal studies have demonstrated dose-dependent detrusor relaxation with beta-3 adrenoceptor agonists during the storage phase of the micturition cycle, as well as inhibition of neurogenic overactivity and experimentally induced OAB, and OAB associated with bladder outlet obstruction.^{19–22} Beta-3 adrenoceptor agonists increase bladder capacity without affecting micturition pressure or residual urine volume.^{5,19} In rats with spinal cord transection, beta-3 adrenoceptors have been demonstrated to directly inhibit afferent nerve activity.⁵ Andersson et al reviewed the published literature on beta adrenoceptors and concluded that stimulation of the beta-3 adrenoceptor relaxes detrusor smooth muscle, decreases afferent signaling from the bladder, improves bladder compliance on filling, and increases bladder capacity.²³

Pharmacokinetics and metabolism

The available formulation of mirabegron is an oral controlled absorption system and its oral bioavailability ranges from 24% to 53%.²⁴ There is substantial interindividual variability in the oral bioavailability of mirabegron, which is dependent on sex and dose. Sex differences in the oral bioavailability of mirabegron were noted in a large single-dose, open-label, randomized, parallel-group, crossover study in 91 subjects that also included females.²⁴ There was a 64% increase in the area under the curve (AUC) in female subjects after oral dosing (25–100 mg) relative to male subjects. A dose-dependent increase in oral bioavailability of mirabegron was observed, from 24% at the 50 mg dose to 45% at the 150 mg dose.²⁴ The increased bioavailability at higher oral doses may be related to the interaction of mirabegron with P-glycoprotein, which is known to act as an intestinal efflux transporter.²⁵ It is postulated that the dose-dependent increase in oral bioavailability may be related to saturation of P-glycoprotein by increasing concentrations of mirabegron in the gut from higher oral doses.^{25,26}

Mirabegron is extensively metabolized by the liver into at least 10 metabolites, none of which appear to be active in the treatment of OAB.²⁷ The terminal elimination half-life ranges

from 26 to 65 hours.²⁸ Mirabegron undergoes several metabolic pathways, including n-dealkylation, oxidative metabolism mediated by cytochrome P450 (CYP)3A4/5,²⁹ with a minor role of CYP2D6, amide hydrolysis by esterases, and glucuronidation mediated by uridine diphosphate glucuronosyltransferases.^{26,27} The CYP2D6 gene is polymorphic and individuals may be stratified into ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers.³⁰ Following a single oral dose of mirabegron (160 mg), the plasma exposure in poor metabolizers was 19% higher than in extensive metabolizers.³⁰ The amount of drug, as a percentage of the dose excreted in the urine was 15.4% + 4.2% in poor metabolizers versus 11.7% + 3.0% in extensive metabolizers, which suggests that poor metabolism of mirabegron in poor metabolizers leads to slightly increased plasma exposure and urinary excretion of the drug.³⁰

Effect of food intake on pharmacokinetic properties of mirabegron

A single-dose, randomized, open-label, three-period, parallel-dose group, crossover study was performed in which a 50 mg or 100 mg mirabegron oral controlled absorption system was administered orally to healthy subjects in the fasted state or after a high-fat or low-fat breakfast. The primary endpoints for assessment of food effects were peak plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf}). With either the fed condition or dose, the 90% confidence intervals (CIs) for the fed/fasted ratios of both peak plasma concentration and AUC_{0-inf} for mirabegron fell below the predetermined range for bioequivalence (80%–115%), suggesting that food had no effect on exposure to the mirabegron oral controlled absorption system. When mirabegron 50 mg or 100 mg was administered with a high-fat breakfast, the C_{max} decreased by about 39%–45%, and the overall exposure as measured by AUC_{0-inf} was decreased by about 17%–18%. A greater decrease was noted with a low-fat breakfast, where mirabegron C_{max} was decreased by about 64%–75% and the AUC_{0-inf} by about 47%–51%.³¹ The prescribing information from the US indicates that mirabegron can be taken with or without food at the approved doses.³²

Effect of renal impairment

An open-label, single-dose, parallel-group study evaluated the effect of renal impairment on mirabegron. This study included age-matched and weight-matched males and females with no impairment of renal function or mild, moderate, or severe impairment based on estimated glomerular filtration

rate. After a single oral dose of mirabegron 100 mg, the geometric mean AUC_{0-inf} was 31%, 66%, and 118% higher in subjects with mild, moderate, and severe renal impairment, respectively. C_{max} increased by 6%, 23%, and 92% in mild, moderate, and severe renal impairment, respectively.²⁵

Effect of hepatic impairment

A study was performed to evaluate the impact of hepatic impairment on mirabegron. The Child-Pugh classification for hepatic function was used to stratify both male and female subjects into healthy subjects with no hepatic impairment or those with mild or moderate impairment. Mild or moderate hepatic impairment was associated with an increase in C_{max} of 9% and 175%, respectively, compared with healthy matched controls.²⁵ The AUC_{0-inf} was increased by 19% and 65% in those with mild or moderate hepatic impairment, respectively, compared with healthy controls.²⁵

Effect of sex and age on pharmacokinetics of mirabegron

Two studies were performed to evaluate the effect of sex and age on the pharmacokinetics of mirabegron.²⁸ The first study was a double-blind, randomized, placebo-controlled, multiple dose-escalation study using six separate dose levels, ie, 50 mg, 100 mg, 200 mg, and 300 mg of the mirabegron oral controlled absorption system for young subjects, and 50 mg and 200 mg for elderly subjects. On day 1 of the study, 12 subjects received a single dose of mirabegron and four subjects received placebo, followed by a 3-day washout and once-daily dosing for 10 days at the selected dose level. The second study was an open-label crossover enrolling 75 healthy subjects, comprising 36 healthy young (18 male and 18 female) and 39 older (21 male and 18 female) subjects stratified by age and sex and randomized to receive one of six treatment sequences, where each subject received two of three possible doses of the mirabegron oral controlled absorption system (25 mg, 50 mg, and 100 mg) in random sequence separated by a minimum of 14 days. Analysis of variance of AUC_{0-inf} and C_{max} following multiple doses of 25–100 mg demonstrated no significant difference between older (>55 years) and younger subjects. However, analysis of variance identified a significant effect of sex on the pharmacokinetics of mirabegron, with significantly higher C_{max} and AUC_{0-inf} (38%–44%), respectively, in women of all age groups compared with men.²⁸ The time taken to reach peak plasma concentration for mirabegron was independent of age in both single-dose and multiple-dose studies.²⁶ The mean

elimination half-life was overall slightly longer in the elderly as well as in women compared with men.

Drug-drug interactions

The ability of mirabegron to inhibit the activity of the most relevant CYP enzymes, including CYP1A1/2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5, was studied in vitro using human liver microsomes.³³ Except for CYP2D6, the in vitro concentration of mirabegron required for mediating the 50% inhibitory concentration (IC_{50}) with and without preincubation amounted to >100 mmol/L,³³ which is 370-fold higher than the C_{max} measured in human pharmacokinetic studies.^{24,28,34} Thus, mirabegron is not expected to have clinically significant drug-drug interactions based on its therapeutic plasma exposure range of 79–630 ng·hour/mL and the high IC_{50} values needed for inhibition of CYP1A1/2, 2B6, 2C8, 2C9, 2C19, 2E1, and 3A4/5.²⁶ In addition to the potential effects of inhibition on CYP2D6, drug interactions may also be the result of the effect of other drugs on efflux transporters, such as P-glycoprotein,³⁵ that plays a role in the bioavailability of mirabegron.²⁴

Ketoconazole

A two-period, one-sequence, crossover study was performed evaluating the interaction of mirabegron with ketoconazole, a CYP3A4 and P-glycoprotein inhibitor, in a group of 24 healthy male (n=12) and female (n=12) adults.³⁶ Individuals received a single dose of mirabegron 100 mg on day 1 in period 1 and on day 4 in period 2, with multiple dosing of ketoconazole 400 mg once daily from day 1 to day 9. The steady-state plasma levels of ketoconazole caused a 1.4-fold and 1.8-fold increase in C_{max} and AUC_{0-inf} , respectively.

Rifampin

The interaction of rifampin, a potent inducer of several CYP enzymes, including CYP3A, 2B6, 2C9, and 2C19 as well as a weak inducer of CYP1A2, uridine diphosphate glucuronosyltransferase, and transporters including P-glycoprotein, with mirabegron was evaluated in a one-sequence, crossover study in 24 healthy adults, comprising 13 males and 11 females.³⁶ This 15-day study evaluated the effect of repeat doses of rifampin 600 mg per day given from day 5 for 10 days onwards on the pharmacokinetics of a single 100 mg dose of mirabegron administered on day 1 and on day 12. Coadministration of rifampin resulted in a 0.35-fold and 0.44-fold decrease in the C_{max} and AUC_{0-inf} of mirabegron, which could be related to induction of P-glycoprotein in the intestine, resulting in reduced oral bioavailability, which is consistent with a lack of effect on the elimination half-life of mirabegron. The amount

of mirabegron as a percentage of the dose excreted in urine decreased from 7.8% to 4.5% in the presence of rifampin.³⁶

Another study evaluated the effect of CYP2D6 inhibition by mirabegron. In this 38-day study, 28 healthy individuals received a single oral dose of 50 mg desipramine on days 1, 18, and 38 of the study. Mirabegron 100 mg was given daily from day 5 to day 23 to achieve steady-state levels. The result was an increase in the elimination half-life of desipramine and a 1.8-fold and 3.4-fold increase in C_{max} and AUC_{0-inf} , respectively.³⁷

When mirabegron is used concomitantly with drugs that are metabolized by CYP2D6, especially those with a narrow therapeutic index (ie, thioridazine, flecainide, and propafenone), appropriate monitoring and possible dose adjustment of such drugs may be necessary.³⁸

Digoxin

When given in combination with digoxin, mirabegron increased the mean C_{max} of digoxin from 1.01 ng/mL to 1.3 ng/mL (29%) and the AUC from 16.7 ng·hour/mL to 19.3 ng·hour/mL (27%). Thus, it is recommended that the lowest dose for digoxin should initially be considered in patients who are starting a combination of mirabegron and digoxin.³⁸

Warfarin

The mean C_{max} of S-warfarin and R-warfarin was increased by approximately 4% and the AUC by approximately 9% when warfarin was administered as a single dose of 25 mg after multiple doses of mirabegron 100 mg; however, there was no effect on the international normalized ratio (INR) or prothrombin time. The effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic endpoints such as INR and prothrombin time has not been fully investigated.³⁸

Oral contraceptives

With multiple dosing of mirabegron 100 mg once daily, there were no changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levonorgestrel, both of which are CYP3A4 substrates).³²

Metformin

Coadministration of metformin 500 mg twice daily with mirabegron immediate-release 160 mg once daily resulted in an approximately 20% decrease in the mean C_{max} and AUC of mirabegron.³² There was no relevant effect of multiple doses of mirabegron immediate-release on the AUC_{0-inf} and C_{max} of metformin.³²

Combination therapy in OAB and benign prostatic hypertrophy

The effect of coadministration of solifenacin 10 mg and mirabegron 100 mg once daily was evaluated in healthy

volunteers. The mean mirabegron C_{max} was not affected by concomitant solifenacin; however, the mean solifenacin C_{max} and AUC_{0-inf} were increased by 23% and 26%, respectively, with concomitant mirabegron. Caution is recommended when combining mirabegron with an antimuscarinic agent to treat OAB because of the risk of urinary retention.³⁸

The cardiovascular results of a study in healthy men 45 years of age and older does not suggest a clinically relevant pharmacodynamic interaction between tamsulosin and mirabegron.³² There were no changes in pulse or systolic blood pressure noted in either treatment arm, and a small decrease in diastolic blood pressure was noted in the combination dosing group compared with each drug alone. There were no serious adverse events and no events of syncope in either treatment arm.³²

Efficacy

Three large-scale, placebo-controlled, Phase III studies evaluated the efficacy and safety of mirabegron compared with placebo using doses of 25 mg, 50 mg, and 100 mg; one study utilized the 25 mg and 50 mg doses (NCT00912964) whereas the others evaluated the 50 mg and 100 mg doses. Study sites were located internationally (NCT00689104 [Europe and Australia],³⁹ NCT00912964 [Europe, the US, Canada],⁴⁰ and NCT00662909 [the US and Canada]).⁴¹ Two of the studies (NCT00689104 and NCT00912964) included tolterodine extended-release 4 mg once daily as an active comparator. Inclusion criteria were identical for all three trials, consisting of both men and women ≥ 18 years of age (the majority female) who were required to have an average micturition frequency of at least eight episodes per 24 hours and at least three episodes of urgency, with or without incontinence, during a 3-day period. The studies excluded patients with stress incontinence or mixed incontinence with predominant stress incontinence and a $>3,000$ mL daily urine volume. The study design consisted of a 2-week, single-blind, placebo run-in period followed by a 12-week treatment period with visits scheduled at 4, 8, and 12 weeks. Efficacy was assessed using 3-day voiding diaries prior to each clinic visit. Coprimary efficacy endpoints were mean change in number of incontinence episodes and micturitions per 24 hours from baseline to final visit. Secondary endpoints included changes in volume voided per micturition, mean number of urgency and urge incontinence episodes, and various quality of life scores, ie, an OAB questionnaire, treatment satisfaction visual analog scale (TS-VAS), and patient perception of bladder condition (Table 1). In the Nitti et al study, significant improvements in all key secondary endpoints were observed for both mirabegron doses versus placebo.⁴¹ Khullar et al also

Table 1 Multi-trial comparisons of coprimary efficacy endpoints and quality of life measures

	Nitti et al ⁴¹			Khullar et al ³⁹			Van Kerrebroeck et al ⁴⁰		
	PBO	Mirabegron 50 mg	Mirabegron 100 mg	PBO	Mirabegron 50 mg	Mirabegron 100 mg	PBO	Mirabegron 25 mg	Mirabegron 50 mg
Coprimary efficacy endpoints									
Incontinence episodes per 24 hours (FAS-I)									
n	325	312	296	291	293	281	262	254	257
Baseline (mean)	3	2.8	2.7	2.67	2.83	2.89	2.43 [§]	2.65 [§]	2.51 [§]
Change from baseline	-1.13	-1.47 [#]	-1.63 [#]	-1.17	-1.57	-1.46	-0.96	-1.36	-1.38
Difference from PBO	NA	-0.34	-0.5	NA	-0.41	-0.29	NA	-0.40	-0.42
95% CI	NA	(-0.66, -0.3) [§]	NR	NA	(-0.72, -0.09)	(-0.61, 0.03)	NA	(-0.74, -0.06) [§]	(-0.76, -0.08) [§]
P value	NA	0.026 [§]	NR	NA	0.003 [#]	0.010 [#]	NA	0.005 [#]	0.001 [#]
Micturitions per 24 hours (FAS)									
n	433	425	412	480	473	478	415	410	426
Baseline (mean)	11.5	11.8	11.7	11.71	11.65	11.51	11.48 [§]	11.68 [§]	11.66 [§]
Change from baseline	-1.05	-1.66 [#]	-1.75 [#]	-1.34	-1.93	-1.77	-1.18	-1.65	-1.60
Difference from PBO	NA	-0.61	-0.70	NA	-0.60	-0.44	NA	-0.47	-0.42
95% CI	NA	NR	NR	NA	(-0.90, -0.29)	(-0.74, -0.13)	NA	(-0.82, -0.13) [§]	(-0.76, -0.08) [§]
P value	NA	NR	NR	NA	<0.001 [#]	0.005 [#]	NA	0.007 [#]	0.015 [#]
Quality of life measures									
Treatment satisfaction visual analog scale (TS-VAS) [¶]									
Mean (SE)	0.70 (0.16)	1.55 (0.16) [‡]	2.09 (0.16) [‡]	1.89 (0.146)	2.55 (0.149) [‡]	2.66 (0.146) [‡]	1.05	1.54 [‡]	1.88 [‡]
Mean diff from PBO (SE)	NR	NR	NR	NA	0.66 (0.208)	0.77 (0.207)	NR	NR	NR
95% CI	(0.4, 1.0)	(1.2, 1.9)	(1.8, 2.4)	NA	(0.25-1.07)	(0.36-1.17)	(0.75, 1.35)	(1.24, 1.84)	(1.58, 2.18)
P value	NA	< 0.05	< 0.05	NA	0.001	< 0.001	NA	0.024	< 0.001
Overactive bladder questionnaire (OAB-q) Symptom Bother Score [¶]									
Mean (SE)	-10.8 (0.97)	-17.0 (0.98) [‡]	-20.2 (0.99) [‡]	-14.9 (0.84)	-19.6 (0.85) [‡]	-19.9 (0.84) [‡]	-16	-17.9 [‡]	-18.8 [‡]
Mean diff from PBO (SE)	NR	NR	NR	NA	-4.17 (1.19)	-5.0 (1.19)	NR	NR	NR
95% CI	(-12.7, -8.9)	(-18.9, -15.1)	(-22.1, -18.2)	NA	(-7.1 to -2.4)	(-7.3 to -2.6)	(-17.8, -14.3)	(-19.6, -16.1)	(-20.5, -17.1)
P-value	NA	< 0.05	< 0.05	NA	< 0.001	< 0.001	NA	0.15	0.028
Patient perception of bladder condition (PPBC) [¶]									
Mean (SE)	-0.5 (0.1)	-0.7 (0.1) [‡]	-0.8 (0.1) [‡]	-0.8 (0.05)	-1.0 (0.06) [‡]	-1.1 (0.05) [‡]	-0.7	-0.8 [‡]	-0.7 [‡]
Mean diff from PBO (SE)	NR	NR	NR	NA	-0.2 (0.08)	-0.2 (0.08)	NR	NR	NR
95% CI	(-0.6, -0.4)	(-0.8, -0.6)	(-0.9, 0.7)	NA	(-0.3 to -0.0)	(-0.4 to -0.01)	(-0.8, -0.6)	(-0.9, -0.6)	(-0.8, -0.6)
P-value	NA	< 0.05	< 0.05	NA	0.045	0.001	NA	0.49	0.64

Notes: Data are adjusted mean changes from baseline generated from the analysis of covariance (ANCOVA) model with treatment group, sex, and geographic region as fixed factors, and baseline as a covariate. Data are for the FAS (full analysis set), except for incontinence outcomes, which are for the FAS-I. P-values are pairwise comparisons versus placebo in the ANCOVA model or stratified rank ANCOVA model for incontinence outcomes. Data from Astellas Prescribing Information;²⁸ Nitti et al;⁴¹ Khullar et al;³⁹ and Van Kerrebroeck et al.⁴⁰ [§]data from Andersson.¹³ [#]P < 0.05 with multiplicity adjustment. [‡]P < 0.05 without multiplicity adjustment. [¶]for TS-VAS an increase in value indicates improvement. For OAB-q Symptom Bother Score and PPBC a decrease in value indicates improvement. **Abbreviations:** PBO, placebo; CI, confidence interval; FAS-I, full analysis set incontinence; FAS, full analysis set; NR, not reported; NA, not applicable; SE, standard error; TS-VAS, treatment satisfaction visual analog scale; OAB-q, overactive bladder questionnaire; PPBC, patient perception of bladder condition.

demonstrated statistically significant improvements in key secondary efficacy endpoints.³⁹

A pooled analysis evaluating the efficacy and safety of mirabegron using these three Phase III studies was recently published.⁴² The efficacy analysis was only performed on 50 mg (all three studies) and 100 mg mirabegron (NCT00662909⁴¹ and NCT00689104³⁹) groups. Coprimary and secondary efficacy endpoints were the same as previously mentioned. Secondary endpoints also included the proportion of “responders”, divided into complete continence, $\geq 50\%$ decrease from baseline in mean number of incontinence episodes/24 hours, and up to eight micturitions/24 hours at final visit (last category determined by post hoc analysis). A statistically significant improvement was noted in mean change from baseline to the final visit with regard to both coprimary endpoints for both 50 mg and 100 mg mirabegron when compared with placebo ($P < 0.05$ for all comparisons). Statistically significant improvements were also seen in both mirabegron groups when compared with placebo for all secondary endpoints, including change from baseline to the final visit in mean volume voided/micturition, change from baseline to week 4 in mean number of incontinence episodes/24 hours, change from baseline to week 4 in mean number of micturitions/24 hours, mean level of urgency, mean number of urgency incontinence episodes/24 hours, mean number of urgency episodes (grade 3/4), change from baseline to final visit in mean number of nocturia episodes/24 hours, and change from baseline to final visit in TS-VAS scores. Responder analysis showed that mirabegron 50 mg and 100 mg were 1.32 (95% CI 1.08–1.61) and 1.58 (95% CI 1.25–2.00) times more likely to achieve complete continence at the final visit compared with placebo ($P < 0.05$). With regards to achieving a $\geq 50\%$ reduction from baseline to final visit in mean number of incontinence episodes/24 hours, 50 mg and 100 mg mirabegron were 1.54 (95% CI 1.26–1.89) and 1.64 (95% CI 1.29–2.07) times more likely to achieve this than placebo, respectively, which was statistically significant ($P < 0.05$). Similar odds ratios also existed for both dose groups with regard to reduction in micturitions at the final visit to $\leq 8/24$ hours ($P < 0.05$). Further statistical analysis was performed for two patient groups, ie, those who discontinued previous antimuscarinic medications (the majority due to insufficient effect) and those who were treatment-naïve. In the patients who had previously used antimuscarinics, both mirabegron 50 mg and 100 mg showed a significant adjusted mean change (95% CI) in mean number of incontinence episodes/24 hours from baseline to final visit, but only the 50 mg group showed a statistically significant difference

compared with placebo, ie, -1.49 ($-1.66, -1.32$) and -0.92 ($-1.09, -0.75$), respectively. Analysis of the other coprimary endpoint, ie, mean number of micturitions/24 hours from baseline to final visit, in patients who previously discontinued antimuscarinics, showed a statistically significant adjusted mean difference (95% CI) in both dosage groups and also when compared with placebo (-0.93 [$-1.12, -0.74$], -1.67 [$-1.86, -1.48$], and -1.61 [$-1.85, -1.37$] for placebo, mirabegron 50 mg, and mirabegron 100 mg, respectively).

A randomized, double-blind, active-controlled, Phase III study was performed to assess the 12-month safety and efficacy of mirabegron 50 mg and 100 mg.⁴⁴ The inclusion criteria and study design were identical to the previous Phase III studies, except that the double-blind treatment period was extended to 12 months. Assessment of efficacy endpoints was done at 1, 3, 6, 9, and 12 months. Tolterodine extended-release 4 mg served as the active control. Improvement in efficacy variables was noted in all three treatment groups, starting at the first visit (month 1) and maintained to month 12. Treatment with mirabegron 100 mg was associated with a numerically greater improvement in efficacy outcomes (mean number of incontinence episodes and micturitions per 24 hours and mean volume voided per micturition). Treatment with tolterodine extended-release 4 mg also led to a reduction in mean number of incontinence episodes and micturitions per 24 hours, and the mean volume voided per micturition was numerically higher than both doses of mirabegron for mean number of incontinence episodes and micturitions per 24 hours at 12 months. Numeric improvements were seen in all three treatment groups for the secondary variables, including the OAB questionnaire, health-related quality of life, patient perception of bladder condition, TS-VAS, and number of nocturia episodes. This study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups.

Combination therapy

Although approved by the US Food and Drug Administration as monotherapy for the treatment of OAB, the unique mechanism of action of mirabegron supports the concept of combination therapy with an anticholinergic agent. A factorial-design, multicenter, randomized, double-blind, parallel-group, placebo/monotherapy-controlled Phase II trial was performed in men and women aged ≥ 18 years with OAB symptoms for at least 3 months.⁴³ The study design involved a 2-week, single-blind, placebo run-in period. Patients with eight or more micturitions per 24 hours and three or more urgency episodes per 72 hours (with or without

incontinence) on a 3-day micturition diary were randomized to one of 12 treatment arms with once-daily treatment for 12 weeks (Table 1).

Mirabegron 25 mg or 50 mg combination therapy with solifenacin 5 mg or 10 mg demonstrated significantly greater efficacy than solifenacin 5 mg alone on change from baseline to end of treatment in mean volume voided per micturition (all dose combinations) and micturition frequency (10 mg +25 mg, 5 mg +50 mg, and 10 mg +50 mg). Statistically significant differences versus placebo were seen on treatment with the solifenacin/mirabegron combinations at doses of 5 mg +50 mg, 10 mg +25 mg, and 10 mg +50 mg.

A post hoc mixed-effect Poisson regression model demonstrated a statistically significant decrease in the mean number of incontinence episodes per 24 hours at the end of treatment versus both placebo and solifenacin 5 mg for the solifenacin/mirabegron combination at doses of 5 +25 mg and 5 mg +50 mg. There was no significant increase in adverse events with the combination treatment compared with mirabegron or solifenacin monotherapy.⁴³

Safety and tolerability

General safety

A randomized, double-blind, active-controlled, Phase III study was performed to assess the 12-month safety and efficacy of mirabegron 50 mg and 100 mg.⁴⁴ The primary safety variable was the incidence and severity of treatment-emergent adverse events. At selected investigational sites, a subset of patients underwent ambulatory blood pressure monitoring, in which blood pressure and heart rate were assessed every 15 minutes during a 24-hour period at baseline and at 6 months and 12 months. Treatment-emergent adverse events were reported

in 59.7% and 61.3% of patients receiving mirabegron 50 mg and 100 mg, respectively. Most of the treatment-emergent adverse events were mild or moderate in severity. The most frequent were hypertension (9.2% and 9.8%), dry mouth (2.8% and 2.3%), constipation (2.8% and 3.0%), and headache (4.1% and 3.2%) for mirabegron 50 mg and 100 mg, respectively. Discontinuation due to adverse events occurred in 6.4% and 5.9%, respectively. Urinary retention occurred in one patient on mirabegron 50 mg and one patient on mirabegron 100 mg. There was no acute urinary retention in the mirabegron 50 mg group. Acute urinary retention requiring catheterization occurred in one patient on mirabegron 100 mg. The incidence of cardiac arrhythmias was 3.9% in the mirabegron 50 mg group and 4.1% in the mirabegron 100 mg group. Adjusted mean changes from baseline to final visit for systolic blood pressure in the mirabegron 50 mg and 100 mg groups were 0.2 mmHg and 0.4 mmHg for morning measurements and -0.3 and 0.1 mmHg for afternoon measurements. Adjusted mean changes for diastolic blood pressure were -0.3 and 0.4 mmHg for morning measurements and -0.0 and 0.1 mmHg for afternoon measurements. The mean change in pulse rate from baseline was 1.6 and 1.5 beats per minute for 100 mg and 50 mg of mirabegron, respectively. No consistent trends in electrocardiographic changes were noted.

A pooled safety analysis of the three randomized, double-blind, placebo-controlled Phase III studies demonstrated the overall incidence of treatment-emergent adverse events to be similar across treatment groups, with no evidence of a dose-response across the groups for overall rates of treatment-emergent adverse events (placebo [47.7%], mirabegron 25 mg [48.6%], mirabegron 50 mg [47.1%], and

Table 2 Reported treatment-related adverse events of mirabegron $\geq 2\%$

Adverse events	Khullar et al ^{39,§}			Nitti et al ^{41,§}			Van Kerrebroeck et al ^{40,#}		
	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Hypertension	7.7%	5.9%	5.4%	6.6%	6.1%	4.9%	8.5%	11.3%	10.7%
Nasopharyngitis	1.6%	2.8%	2.8%	2.9%	3.4%	2.5%	3.2%	3.5%	5.7%
Dry mouth	2.6%	2.8%	2.8%	1.5%	0.5%	2.1%	*	*	*
Headache	2.8%	3.7%	1.8%	2.0%	3.2%	3.0%	4.4%	2.1%	2.7%
Influenza	1.6%	2.2%	2.0%	NR	NR	NR	NR	NR	NR
Sinusitis	NR	NR	NR	2.2%	2.0%	2.1%	NR	NR	NR
Upper respiratory tract infection	*	*	*	2.5%	2.7%	2.1%	1.3%	2.1%	1.6%
Urinary tract infection	*	*	*	1.8%	2.7%	3.7%	3.3%	4.2%	4.8%
Diarrhea	NR	NR	NR	1.3%	2.7%	2.1%	NR	NR	NR

Notes: *Reported but <2% for treatment groups; §includes events reported from first dose of double-blind treatment until 30 days after the last dose of double-blind study drug; #includes events reported from first dose of double-blind treatment until 14 days after the last dose of double-blind study drug.

Abbreviation: NR, not reported.

mirabegron 100 mg [43.3%]).⁴² The most common drug-related treatment-emergent adverse events in the mirabegron groups were hypertension and headache, which were of similar incidence to that with placebo and tolterodine, except for dry mouth, which was at the placebo level for mirabegron (Table 2). The proportion of patients discontinuing the study drug because of treatment-emergent adverse events was low and similar across the groups (placebo [2.1%], mirabegron 25 mg [1.6%], mirabegron 50 mg [2.1%], and mirabegron 100 mg [2.8%]). The adjusted mean difference versus placebo for change from baseline to final visit in systolic and diastolic blood pressure (morning and afternoon measurements) was minimal and comparable across the mirabegron groups. The adjusted mean difference versus placebo for change from baseline to final visit in pulse rate (morning and afternoon measurements) demonstrated a dose-dependent increase from 0.6 to 2.3 beats per minute in the mirabegron groups. Tachycardia, based on treatment-emergent adverse events and/or observations of pulse rate >100 beats per minute captured by patient diary, was less than 5% in each mirabegron treatment group and comparable with placebo. Electrocardiographic studies did not demonstrate any overt trends in central tendency or categoric outliers for QTc interval assessment across treatment groups. Changes in laboratory values were small and comparable across the treatment groups. The incidence of urinary retention was infrequent in the studies and less in the mirabegron-treated patients than in placebo-treated patients. The mean change in post-void residual from baseline to final visit was unremarkable, and the proportion of patients with a change in post-void residual of >150 mL from baseline was lower in the mirabegron group compared with the placebo group.

Postmarketing, there have been reports of urinary retention with mirabegron, although Chapple et al⁴⁵ reported no episodes of acute urinary retention in the BLOSSOM trial, nor were there any reported by Chapple et al in the DRAGON trial.⁴⁶

Ocular safety

Muscarinic receptors are present in the eye, where they mediate the contractility response and are involved in the autonomic control of the iris sphincter.⁴⁷ Muscarinic antagonists with an affinity for the M3 receptor can have ocular effects, such as mydriasis, loss of accommodation, and narrowing of the anterior chamber. The antimuscarinic agents approved for the treatment of OAB are contraindicated in patients with uncontrolled narrow angle glaucoma, and caution is recommended regarding their use in treated narrow angle glaucoma. The role of beta-3 adrenoceptors in the eye is not fully understood.

In vitro studies have demonstrated that the beta-adrenergic relaxation response in the bovine iris sphincter appears to be mediated by a mixed population of beta-adrenergic receptors, including beta-3 adrenoceptors. Additional animal studies have demonstrated the presence of beta-3 adrenoceptors in mouse conjunctival epithelial cells^{48,49} and choroidal and retinal endothelial cells,^{50,51} and their involvement in the control of retinal vascular tone in rats.⁵²

An 8-week, randomized, double-masked, placebo-controlled study was performed to assess the ocular safety of mirabegron in healthy volunteers.⁵³ Individuals were randomized 1:1 to a suprathreshold dose of oral mirabegron 100 mg or placebo once daily for 56 days. Intraocular pressure was measured at screening, baseline, day 10, and day 56 (end of treatment) using Goldmann applanation tonometry. Visual acuity and biomicroscopy were also evaluated. The primary endpoint was mean change from baseline in intraocular pressure at 56 days or end of treatment with mirabegron versus placebo. Secondary outcome variables included change from baseline to day 10 in intraocular pressure, and increases in intraocular pressure of >6 mmHg and >10 mmHg in either eye from baseline to day 10 and day 56. For the primary endpoint, mirabegron was noninferior to placebo, based on the prespecified limit of 1.5 mmHg. No statistically significant treatment effects on intraocular pressure were seen at day 10. Changes in visual acuity and biomicroscopy were not suggestive of a mirabegron effect. Further, no treatment-emergent adverse event of glaucoma was reported.

Cardiovascular safety

International Conference on Harmonisation E14 guidance⁵⁴ requires a thorough QT/QTc (heart rate-corrected QT interval) study for all new drugs, including at supraphysiologic doses. Animal studies with mirabegron have demonstrated no inhibitory effect towards ion channels (including *ether-à-go-go*-related gene), action potential duration, or transmural repolarization.³⁴ Since mirabegron increases heart rate at suprathreshold doses (>50 mg), the QTc study used individual subject-specific correction formula (QTcIs⁵⁵ with adaptation for heart rate hysteresis)⁵⁶ instead of the commonly used Fridericia's (QTcF) correction because Fridericia's correction does not provide accurate QTc values in the presence of drug-induced changes in heart rate.⁵⁷ Three hundred and fifty-two subjects received at least one dose of study medication, and pharmacokinetic and pharmacodynamic analyses were performed on 333 and 317 subjects, respectively.³⁴ An equal number of males and females were enrolled in each group. The study design was a four-arm, parallel, two-way crossover study, which was double-blind,

as well as placebo-controlled and active (moxifloxacin)-controlled. Two baseline electrocardiograms were obtained, and patients were then randomized to one of eight treatment sequences of placebo crossover with once-daily (10 days) 50 mg, 100 mg, or 200 mg mirabegron or a single 400 mg moxifloxacin dose on day 10. During each period, continuous electrocardiograms were recorded at two baselines and on the last drug administration day. The primary variable was the time-matched baseline-adjusted QTcI difference ($\Delta\Delta\text{QTcI}$) between individual mirabegron doses and placebo by sex. The mean $\Delta\Delta\text{QTcI}$ increased at higher mirabegron doses, with a greater effect in females than in males. In both genders, at the 50 mg therapeutic dose, the mean $\Delta\Delta\text{QTcI}$ was below 5 msec at all time points, and the upper bound of the one-sided 95% CI did not exceed 10 msec. However, at the supratherapeutic 100 mg dose, the mean $\Delta\Delta\text{QTcI}$ was above 5 msec at various time points for women only, and in both genders, the upper bound of the one-sided 95% CI did not exceed 10 msec. The supratherapeutic 200 mg dose did not exceed 10 msec in men, but did exceed 10 msec in women at various time points. Thus, at the therapeutic dose of 50 mg and the supratherapeutic dose of 100 mg, according to the International Conference on Harmonisation E14 criteria, mirabegron did not prolong the QTcI interval.³⁴ In this study, the maximum mean increase in supine systolic/diastolic blood pressure at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mmHg greater than on placebo. The 24-hour average increase in systolic blood pressure compared with placebo was 3.0 mmHg, 5.5 mmHg, and 9.7 mmHg at mirabegron doses of 50 mg, 100 mg, and 200 mg, respectively. Increases in diastolic blood pressure were dose-dependent, but were smaller than for systolic blood pressure.

Phase I studies demonstrated a mirabegron-related, dose-responsive increase in blood pressure of approximately 3–4 mmHg at C_{max} . In Phase III studies, mirabegron-related increases in systolic and diastolic blood pressure were only about 1 mmHg. A similar discordance was seen between the increases in heart rate in Phase I and Phase III studies, and the reasons for these different results are not clear.¹⁹

Malignancy

The Phase II studies reported an increased incidence of a variety of neoplasms in the mirabegron 100 mg group compared with the placebo group. This increased incidence was not seen with patients receiving mirabegron 50 mg, and it is unclear if there is a true mirabegron-related effect.^{19,32} In the long-term European Union/North American trials, the overall incidence of neoplasms was 0.9% in patients treated

with mirabegron 100 mg and 0% in those treated with mirabegron 50 mg.³²

Tolerability

The more common side effects of mirabegron differ from those of the antimuscarinics, reflecting the different mechanisms of action of these agents. The more common side effects, ie, those occurring in >2% of patients, in the Phase III registration trials are shown in Table 2, with notably higher rates of urinary tract infection and nasopharyngitis in the mirabegron groups compared with placebo.^{39–41} The incidence of dry mouth was comparable with that on placebo and less than that in the tolterodine group (data not shown).

Patient-centered factors

With regard to health-related quality of life outcomes, a pooled analysis of the Phase III studies demonstrated that mirabegron 50 mg and 100 mg were associated with a statistically significant improvement in TS-VAS score compared with placebo ($P<0.05$) at the final visit.⁴² The TS-VAS is a quantitative instrument assessing subjective improvement in patients with OAB. A score of 10 on the TS-VAS indicates complete satisfaction, whereas a positive change from baseline indicates improvement. The adjusted mean (95% CI) changes from baseline to the final visit were 1.25 (1.08–1.42), 2.01 (1.84–2.19), and 2.33 (2.11–2.55) for the placebo, mirabegron 50 mg, and 100 mg groups, respectively (Table 1).⁴² Statistically significant improvements in the OAB questionnaire and patient perception of bladder condition were also noted for mirabegron 50 mg and 100 mg in all three Phase III trials, except for the trial reported by Van Kerrebroeck et al,⁴⁰ which did not show a statistically significant change from baseline in patient perception of bladder condition for mirabegron 50 mg (Table 1).

Conclusion

The increasing prevalence of OAB combined with low long-term patient compliance with antimuscarinic agents indicates a need for alternative treatment options. Mirabegron represents such an alternative by selectively targeting beta-3 adrenoceptors within the bladder to promote filling during the storage phase without inhibiting contractions during micturition. Pharmacokinetic studies do not preclude food consumption while taking mirabegron, although the dosage should be adjusted for severe renal or hepatic impairment. Inhibition of CYP enzymes has been shown, so care should be taken when administering mirabegron with digoxin or metoprolol. Recently completed Phase III studies show

significant improvement in both the number of incontinence episodes and the mean number of micturitions per 24 hours, as well as in validated disease specific patient questionnaires over placebo. Few studies have been performed with active controls, although the current data suggest long-term effects comparable with those of the antimuscarinic agents. The drug is well tolerated with minor adverse effects, most notably a lower rate of dry mouth compared with the antimuscarinics, making mirabegron a reasonable treatment option in patients unable to tolerate first-line medical therapy.

Disclosure

The authors report no conflict of interests in this work.

References

- Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003;20(6):327–336.
- Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol.* 2006;50(6): 1306–1315.
- Coyne KS, Sexton CC, Thompson CL, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. *BJU Int.* 2009; 104(3):352–360.
- Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. *BJU Int.* 2011; 108(7):1132–1138.
- Kanai A, Andersson KE. Bladder afferent signaling: recent findings. *J Urol.* 2010;183(4):1288–1295.
- Andersson KE. LUTS treatment: future treatment options. *NeuroUrol Urodyn.* 2007;26(Suppl 6):943–947.
- Cerruto MA, Asimakopoulos AD, Artibani W, et al. Insight into new potential targets for the treatment of overactive bladder and detrusor overactivity. *Urol Int.* 2012;89(1):1–8.
- Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatments of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. May 2012. Available from: <http://www.auanet.org/education/guidelines/overactive-bladder.cfm>. Accessed July 4, 2013.
- Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. *BJU Int.* 2007;100(5):987–1006.
- Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol.* 2008;54(3):543–562.
- Andersson KE, Chapple CR, Cardozo L, et al. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Curr Opin Urol.* 2009;19(4):380–394.
- Jundt K, Schreyer K, Friese K, Peschers U. Anticholinergic therapy: do the patients take the pills prescribed? *Arch Gynecol Obstet.* 2010; 284(3):663–666.
- Andersson KE. New developments in the management of overactive bladder: focus on mirabegron and onabotulinumtoxin A. *Ther Clin Risk Manag.* 2013;9:161–170.
- Aizawa N, Homma Y, Igawa Y. Effects of mirabegron, a novel beta-3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. *Eur Urol.* 2012;62(6):1165–1173.
- Abrams O, Cardozo L, Khoury S, Wein A, editors. Incontinence. 4th Edition. International Consultation on Incontinence, Paris, France, July 2008. Plymouth, UK Health Publications Ltd, 2009. 631–699.
- Takeda M, Obara K, Mizusawa T, et al. Evidence for beta-3-AR subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. *J Pharmacol Exp Ther.* 1999;288(3):1367–1373.
- Takeda H, Yamazaki Y, Akahane M, Igawa Y, Ajisawa Y, Nishizawa O. Role of the beta-3-AR in urine storage in the rat: comparison between the selective beta-3-AR agonists, CL316, 243, and various smooth muscle relaxants. *J Pharmacol Exp Ther.* 2000;293(3): 939–945.
- Igawa Y, Aizawa N, Homma Y. Beta 3-adrenoceptor agonists: possible role in the treatment of overactive bladder. *Korean J Urol.* 2010;51(12): 811–818.
- Sacco E, Bientinesi R. Mirabegron: a review of recent data and its prospects in the management of overactive bladder. *Ther Adv Urol.* 2012;4(6):315–324.
- Woods M, Carson N, Norton N, Sheldon J, Argentieri T. Efficacy of the beta-3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. *J Urol.* 2001;166(3):1142–1147.
- Hicks A, McCafferty GP, Riedel E, et al. GW427353 (solabegron), a novel, selective beta 3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. *J Pharmacol Exp Ther.* 2007;323(1):202–209.
- Takasu T, Ukai M, Sato S, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-(2-(2-hydroxy-2-phenylthyl)amino)ethyl)acetanilide (YM178), a novel selective beta 3-adrenoceptor agonist on bladder function. *J Pharmacol Exp Ther.* 2007;321(2):642–647.
- Andersson KE, Martin N, Nitti V. Selective β_3 -adrenoceptor agonists in the treatment of the overactive bladder. *J Urol.* February 28, 2013. [Epub ahead of print.]
- Eltink C, Lee J, Schaddelee M, et al. Single dose pharmacokinetics and absolute bioavailability of mirabegron, a β_3 -adrenoceptor agonist for treatment of overactive bladder. *Int J Clin Pharmacol Ther.* 2012;50(11):838–850.
- Dickinson J, Lewand M, Sawamoto T, et al. Effect of renal or hepatic impairment on the pharmacokinetics of mirabegron. *Clin Drug Investig.* 2013;33(1):11–23.
- Kashyap M, Tyagi P. The pharmacokinetic evaluation of mirabegron as an overactive bladder therapy option. *Expert Opin Drug Metab Toxicol.* 2013;9(5):617–627.
- Takusagawa S, van Lier JJ, Suzuki K, et al. Absorption, metabolism and excretion of [(14)C] mirabegron (YM178), a potent and selective β_3 -adrenoceptor agonist, after oral administration to healthy male volunteers. *Drug Metab Dispos.* 2012;40(4):815–824.
- Krauwinkel W, van Dijk J, Schaddelee M, et al. Pharmacokinetic properties of mirabegron, a β_3 -adrenoceptor agonist: results from two phase I, randomized, multiple-dose studies in healthy young and elderly men and women. *Clin Ther.* 2012;34(10):2144–2160.
- Takusagawa S, Yajima K, Miyashita A, Uehara S, Iwatsubo T, Usui T. Identification of human cytochrome P450 isoforms and esterases involved in the metabolism of mirabegron, a potent and selective β_3 -adrenoceptor agonist. *Xenobiotica.* 2012;42(10): 957–967.
- van Gelderen EM, Li Q, Meijer J, et al. An explanatory comparison of the single dose pharmacokinetics of the beta-3-adrenoceptor agonist mirabegron in healthy CYP2D6 poor and extensive metabolizers. *Clin Pharmacol Ther.* 2009;8 Suppl 1:s88 Abstract PIII.
- Lee J, Zhang W, Moy S, et al. Effects of food intake on the pharmacokinetic properties of mirabegron oral controlled-absorption system: a single-dose, randomized, crossover study in healthy adults. *Clin Ther.* 2013;35(3):333–341.

32. Advisory Committee Briefing Document. Mirabegron (YM178) for the treatment of overactive bladder, April 5, 2012. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM298285.pdf>. Accessed September 6, 2013.
33. Takusagawa S, Miyashita A, Iwatsubo T, Usui T. In vitro inhibition and induction of human cytochrome P450 enzymes by mirabegron, a potent and selective β_3 -adrenoceptor agonist. *Xenobiotica*. 2012;42(12):1187–1196.
34. Malik M, van Gelderen EM, Lee JH, et al. Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. *Clin Pharmacol Ther*. 2012;92(6):696–706.
35. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet*. 2003;42(1):59–98.
36. Lee J, Moy S, Meijer J, et al. Role of cytochrome p450 isoenzymes 3A and 2D6 in the in vivo metabolism of mirabegron, a B 3-adrenoceptor agonist. *Clin Drug Investig*. 2013;33(6):429–440.
37. Krauwinkel WJ, van Gelderen EM, Groen MJ. An open-label, one-sequence crossover study to evaluate the effect of multiple doses of mirabegron on the pharmacokinetics of the CYP2D6 substrate desipramine in healthy subjects. Abstract PIII-65 presented at the American Society for Clinical Pharmacology and Therapeutics Annual Meeting, March 17–20, 2010, Atlanta, GA.
38. Myrebriq (mirabegron) prescribing information. Northbrook, IL: Astellas Pharma US Inc; June 28, 2012. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202611s0001bl.pdf. Accessed June 8, 2013.
39. Khullar V, Amarenco G, Angulo JC, 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(2):283–295.
40. Van Kerrebroeck P, Barkin J, Castro-Diaz D, et al. Randomised, double-blind, placebo-controlled Phase III study to assess the efficacy and safety of mirabegron 25 mg and 50 mg once daily in overactive bladder (OAB). Presented at the 42nd Annual Meeting of the International Continence Society, October 15–19, 2012, Beijing, China.
41. 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(4):1388–1395.
42. Nitti VW, Khullar V, van Kerrebroeck P, et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomized, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract*. 2013;67(7):619–632.
43. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with OAB – efficacy results from a phase II study (SYMPHONY). Abstract 1958 presented at the American Urological Association Annual Meeting, May 4–8, 2013 San Diego, CA.
44. Chapple CR, Kaplan, SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β_3 -adrenoceptor agonist, in overactive bladder. *Eur Urol*. 2013;63(2):296–305.
45. Chapple C, Yamaguchi O, Ridder A, et al. Clinical proof of concept study (BLOSSOM) shows novel β_3 adrenoceptor agonist YM 178 is effective and well tolerated in the treatment of symptoms of overactive bladder. *Eur Urol*. 2008b;Suppl 7:239(Abstr 674).
46. Chapple CR, Dvorak V, Radziszewski P, et al; Dragon Investigator Group. A phase II dose-ranging study of mirabegron in patients with overactive bladder. *Int Urogynecol J*. 2013;24(9):1447–1458.
47. Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol*. 2006;148(5):565–578.
48. Enriquez de Salamanca A, Siemasko KF, Diebold Y, et al. Expression of muscarinic and adrenergic receptors in normal human conjunctival epithelium. *Invest Ophthalmol Vis Sci*. 2005;46(2):504–513.
49. Diebold Y, Rios JD, Hodges RR, Rawe I, Dartt DA. Presence of nerves and their receptors in mouse and human conjunctival goblet cells. *Invest Ophthalmol Vis Sci*. 2001;42(10):2270–2282.
50. Steinle JJ, Booz GW, Meininger CJ, Day JN, Granger HJ. Beta 3-adrenergic receptors regulate retinal endothelial cell migration and proliferation. *J Biol Chem*. 2003;278(23):20681–20686.
51. Steinle JJ, Zamora DO, Rosenbaum JT, Granger HJ. Beta 3-adrenergic receptors mediate choroidal endothelial cell invasion, proliferation, and cell elongation. *Exp Eye Res*. 2005;80(1):83–91.
52. Mori A, Nakahara T, Sakamoto K, Ishii K. Role of β_3 -adrenoceptors in regulation of retinal vascular tone in rats. *Naunyn Schmiedeberg Arch Pharmacol*. 2011;384(6):603–608.
53. Novack GD, Lewis RA, Vogel R, et al. Randomized, double-masked, placebo-controlled study to assess the ocular safety of mirabegron in healthy volunteers. *J Ocul Pharmacol Ther*. 2013;29(7):674–680.
54. www.fda.gov/downloads/.../guidances/ucm129357.pdf. Accessed September 22, 2013.
55. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implication for heart rate correction of the QT interval. *Heart*. 2002;87(3):220–228.
56. Malik M, Hnatkova K, Novotny T, Schmidt G. Subject-specific profiles of QT/RR hysteresis. *Am J Physiol Heart Circ Physiol*. 2008;295(6):H2356–H2363.
57. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. *Ann Noninvasive Electrocardiol*. 2003;8(4):343–351.

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