Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mirabegron Teva 50 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of mirabegron.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Mirabegron Teva 50 mg Prolonged-release Tablets
Light yellow approximately 6 × 13 mm oblong, biconvex film coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults (including elderly patients)
The recommended dose is 50 mg once daily.

Special populations

Renal and hepatic impairment
Mirabegron 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 mirabegron in subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see sections 4.4, 4.5 and 5.2).

Table 1: Daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors

		Strong CYP3A inhibitors(3)	
		Without inhibitor	With inhibitor
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 see section 4.5

Patients treated with the 25 mg dose should be advised to use other medicinal products containing mirabegron 25 mg available on the market. The tablet of 50 mg is not intended to be divided to obtain the 25 mg dose.

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 with liquids, swallowed whole and is not to be chewed, divided, or crushed, as it may impact it's characteristics. Mirabegron Teva may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg.

4.4 Special warnings and precautions for use

Renal impairment

Mirabegron has not been studied in patients with end stage renal disease (GFR <15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study (see section 5.2) a dose reduction to mirabegron 25 mg is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hepatic impairment

Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hypertension

Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients.

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

Mirabegron, 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.

Patients with bladder outlet obstruction and patients taking antimuscarinic medicinal products for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medicinal products for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with mirabegron; however, mirabegron should be administered with caution to patients with clinically significant BOO. This medicinal product should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data

Mirabegron is transported and metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and timedependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations.

In vivo data

Drug-drug interactions
The effect of co-administered medicinal products on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of other medicinal products was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron given as oral controlled absorption system (OCAS) tablets. Interaction studies of mirabegron with metoprolol and with metformin used mirabegron immediate-release (IR) 160 mg.

Clinically relevant drug interactions between mirabegron and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.

Effect of enzyme inhibitors
Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose-adjustment is needed when mirabegron is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to 89 mL/min/1.73 m^2) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is mirabegron 25 mg once daily with or without food (see section 4.2).
Mirabegron is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see sections 4.2 and 4.4).

Effect of enzyme inducers
Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of mirabegron. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

Effect of CYP2D6 polymorphism
CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron (see section 5.2). Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Effect of mirabegron on CYP2D6 substrates
In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in C_{max} and a 241% increase in AUC of a single dose of desipramine.

Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated.

Effect of mirabegron on transporters
Mirabegron is a weak inhibitor of P-gp. Mirabegron increased C_{max} and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when this medicinal product is combined with sensitive P-gp substrates e.g. dabigatran.

Other interactions

No clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of solifenacin, tamsulosin, warfarin, metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose-adjustment is not recommended.

Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential

Mirabegron Teva is not recommended in women of childbearing potential not using contraception.

Pregnancy

There is limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). This medicinal product is not recommended during pregnancy.

Breast-feeding

Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk (see section 5.3). No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child.

Mirabegron Teva should not be administered during breast-feeding.

Fertility

There were no treatment-related effects of mirabegron on fertility in animals (see section 5.3). The effect of mirabegron on human fertility has not been established.

4.7 Effects on ability to drive and use machines

Mirabegron Teva has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of mirabegron was evaluated in 8 433 patients with OAB, of which 5 648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received mirabegron for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with this medicinal product, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity.

The most common adverse reactions reported for patients treated with mirabegron 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving mirabegron 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving mirabegron 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving mirabegron 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving mirabegron 50 mg. Serious adverse reactions included atrial fibrillation (0.2%).

Adverse reactions 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 3 double blind, placebo controlled studies.

Tabulated list of adverse reactions

The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies.

The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1 000 to <1/100); rare (≥ 1/10 000 to <1/1 000); very rare (< 1/10 000) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System organ class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis			
Psychiatric disorders					Insomnia* Confusional state*
Nervous system disorders	Headache* Dizziness*				
Eye disorders			Eyelid oedema		
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation			
Vascular disorders				Hypertensive crisis*	
Gastrointestinal disorders	Nausea* Constipation* Diarrhoea*	Dyspepsia Gastritis	Lip oedema		
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura Angioedema*		
Musculoskeletal and connective tissue disorders		Joint swelling			
Renal and urinary disorders			Urinary retention*		
Reproductive system and breast disorders		Vulvovaginal pruritus			
Investigations		Blood pressure increased GGT increased AST increased ALT increased			

*observed during post-marketing experience

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 beats per minute (bpm) (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers.

Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence, ATC code: G04BD12.

Mechanism of action
Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cyclic adenosine monophosphate (cAMP) concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. Mirabegron increased mean voided volume per micturition and decreased the frequency of non-voiding contractions, without affecting voiding pressure, or residual urine in rat models of bladder overactivity. In a monkey model, mirabegron showed decreased voiding frequency. These results indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

During the urine storage phase, when urine accumulates in the bladder, sympathetic nerve stimulation predominates. Noradrenaline is released from nerve terminals, leading predominantly to beta adrenoceptor activation in the bladder musculature, and hence bladder smooth muscle relaxation. During the urine voiding phase, the bladder is predominantly under parasympathetic nervous system control. Acetylcholine, released from pelvic nerve terminals, stimulates cholinergic M2 and M3 receptors, inducing bladder contraction. The activation of the M2 pathway also inhibits beta 3-adrenoceptor induced increases in cAMP. Therefore beta 3-adrenoceptor stimulation should not interfere with the voiding process. This was confirmed in rats with partial urethral obstruction, where mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume.

Pharmacodynamic effects

Urodynamics
Mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks in men with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) showed no effect on cystometry parameters and was safe and well tolerated. The effects of mirabegron on maximum flow rate and detrusor pressure at maximum flow rate were assessed in this urodynamic study consisting of 200 male patients with LUTS and BOO. Administration of mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate. In this study in male patients with LUTS/BOO, the adjusted mean (SE) change from baseline to end of treatment in post void residual volume (mL) was 0.55 (10.702), 17.89 (10.190), 30.77 (10.598) for the placebo, mirabegron 50 mg and mirabegron 100 mg treatment groups.

Effect on QT interval
Mirabegron at doses of 50 mg or 100 mg had no effect on the QT interval individually corrected for heart rate (QTcI interval) when evaluated either by sex or by the overall group.

A thorough QT (TQT) study (n=164 healthy male and n=153 healthy female volunteers with a mean age of 33 years) evaluated the effect of repeat oral dosing of mirabegron at the indicated dose (50 mg once daily) and two supra-therapeutic doses (100 and 200 mg once daily) on the QTcI interval. The supra-therapeutic doses represent approximately 2.6- and 6.5-fold the exposure of the therapeutic dose, respectively. A single 400 mg dose of moxifloxacin was used as a positive control. Each dose level of mirabegron and moxifloxacin was evaluated in separate treatment arms each including placebo-control (parallel cross-over design). For both males and females administered mirabegron at 50 mg and 100 mg, the upper bound of the one-sided 95% confidence interval did not exceed 10 msec at any time point for the largest time-matched mean difference from placebo in the QTcI interval. In females administered mirabegron at the 50 mg dose, the mean difference from placebo on QTcI interval at 5 hours post dose was 3.67 msec (upper bound of the one-sided 95% CI 5.72 msec). In males, the difference was 2.89 msec (upper bound of the one-sided 95% CI 4.90 msec). At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 msec at any time point in males, while in females the upper bound of the one-sided 95% confidence interval did exceed 10 msec between 0.5-6 hours, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the one-sided 95% CI 13.44 msec). Results for QTcF and QTcIf were consistent with QTcI.

In this TQT study, mirabegron increased heart rate on ECG in a dose dependent manner across the 50 mg to 200 mg dose range examined. The maximum mean difference from placebo in heart rate ranged from 6.7 bpm with mirabegron 50 mg up to 17.3 bpm with mirabegron 200 mg in healthy subjects.

Effects on pulse rate and blood pressure in patients with OAB
In OAB patients (mean age of 59 years) across three 12-week phase 3 double blind, placebo controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in systolic blood pressure/diastolic blood pressure (SBP/DBP) was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment.

Effect on intraocular pressure (IOP)
Mirabegron 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of mirabegron on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of mirabegron 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; the upper bound of the two-sided 95% CI of the treatment difference between mirabegron 100 mg and placebo was 0.3 mm Hg.

Clinical efficacy and safety

Efficacy of mirabegron was evaluated in three phase 3 randomized, double blind, placebo controlled, 12-week studies for the treatment of overactive bladder with symptoms of urgency and frequency with or without incontinence. Female (72%) and male (28%) patients with a mean age of 59 years (range 18 - 95 years) were included. The study population consisted of approximately 48% antimuscarinic treatment naïve patients as well as approximately 52% patients previously treated with antimuscarinic medicinal products. In one study, 495 patients received an active control (tolterodine prolonged release formulation).

The co-primary efficacy endpoints were (1) change from baseline to end of treatment in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment in mean number of micturitions per 24 hours based on a 3-day micturition diary. Mirabegron demonstrated statistically significant larger improvements compared to placebo for both co-primary endpoints as well as secondary endpoints (see Tables 2 and 3).

Table 2: Co-primary and selected secondary efficacy endpoints at end of treatment for pooled studies

Parameter	**Pooled studies (046, 047, 074)**	
	Placebo	**Mirabegron 50 mg**
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)		
n	878	862
Mean baseline	2.73	2.71
Mean change from baseline†	-1.10	-1.49
Mean difference from placebo† (95% CI)	--	-0.40 (-0.58, -0.21)
p-value	--	<0.001#
Mean number of micturitions per 24 hours (FAS) (Co-primary)		
n	1328	1324
Mean baseline	11.58	11.70
Mean change from baseline†	-1.20	-1.75
Mean difference from placebo† (95% CI)	--	-0.55 (-0.75, -0.36)
p-value	--	<0.001#
Mean volume voided (mL) per micturition (FAS) (Secondary)		
n	1328	1322
Mean baseline	159.2	159.0
Mean change from baseline†	9.4	21.4
Mean difference from placebo† (95% CI)	--	11.9 (8.3, 15.5)
p-value	--	<0.001#
Mean level of urgency (FAS) (Secondary)		
n	1325	1323
Mean baseline	2.39	2.42
Mean change from baseline†	-0.15	-0.26
Mean difference from placebo† (95% CI)	--	-0.11 (-0.16, -0.07)
p-value	--	<0.001#
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)		

n	858	834
Mean baseline	2.42	2.42
Mean change from baseline†	-0.98	-1.38
Mean difference from placebo† (95% CI)	--	-0.40 (-0.57, -0.23)
p-value	--	<0.001#
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)		
n	1324	1320
Mean baseline	5.61	5.80
Mean change from baseline†	-1.29	-1.93
Mean difference from placebo† (95% CI)	--	-0.64 (-0.89, -0.39)
p-value	--	<0.001#
Treatment satisfaction – visual analogue scale (FAS) (Secondary)		
n	1195	1189
Mean baseline	4.87	4.82
Mean change from baseline†	1.25	2.01
Mean difference from placebo† (95% CI)	--	0.76 (0.52, 1.01)
p-value	--	<0.001*

Pooled studies consisted of studies 046 (Europe/Australia), 047 (North America [NA]) and 074 (Europe/NA).
† Least squares mean adjusted for baseline, gender, and study.
* Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustment.
# Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.
FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.
CI: Confidence Interval

Table 3: Co-primary and selected secondary efficacy endpoints at end of treatment for studies 046, 047 and 074

Parameter	**Study 046**			**Study 047**		**Study 074**	
	Placebo	**Mirabegron 50 mg**	**Tolterodine ER 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)							
n	291	293	300	325	312	262	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.51
Mean change from baseline†	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.38
Mean difference from placebo†	--	-0.41	-0.10	--	-0.34	--	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.76, -0.08)
p-value	--	0.003#	0.11	--	0.026#	--	0.001#
Mean number of micturitions per 24 hours (FAS) (Co-primary)							
n	480	473	475	433	425	415	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.66
Mean change from baseline†	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.60
Mean difference from placebo†	--	-0.60	-0.25	--	-0.61	--	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.76, -0.08)
p-value	--	<0.001#	0.11	--	0.001#	--	0.015#
Mean volume voided (mL) per micturition (FAS) (Secondary)							

n	480	472	475	433	424	415	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	159.3
Mean change from baseline†	12.3	24.2	25.0	7.0	18.2	8.3	20.7
Mean difference from placebo†	--	11.9	12.6	--	11.1	--	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(6.3, 18.6)
p-value	--	<0.001#	<0.001*	--	0.001#	--	<0.001#
Mean level of urgency (FAS) (Secondary)							
n	480	472	473	432	425	413	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.41
Mean change from baseline†	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.29
Mean difference from placebo†	--	-0.09	-0.07	--	-0.11	--	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.22, -0.06)
p-value	--	0.018*	0.085	--	0.004*	--	<0.001‡
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)							
n	283	286	289	319	297	256	251
Mean baseline	2.43	2.52	2.37	2.56	2.42	2.24	2.33
Mean change from baseline†	-1.11	-1.46	-1.18	-0.89	-1.32	-0.95	-1.33
Mean difference from placebo†	--	-0.35	-0.07	--	-0.43	--	-0.39
95% Confidence Interval	--	(-0.65, -0.05)	(-0.38, 0.23)	--	(-0.72, -0.15)	--	(-0.69, -0.08)
p-value	--	0.003*	0.26	--	0.005*	--	0.002‡
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)							
n	479	470	472	432	424	413	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.80
Mean change from baseline†	-1.65	-2.25	-2.07	-0.82	-1.57	-1.35	-1.94
Mean difference from placebo†	--	-0.60	-0.42	--	-0.75	--	-0.59
95% Confidence Interval	--	(-1.02, -0.18)	(-0.84, 0.00)	--	(-1.20, -0.30)	--	(-1.01, -0.16)
p-value	--	0.005*	0.050*	--	0.001*	--	0.007‡
Treatment satisfaction – visual analogue scale (FAS) (Secondary)							
n	428	414	425	390	387	377	388
Mean baseline	4.11	3.95	3.87	5.5	5.4	5.13	5.13
Mean change from baseline†	1.89	2.55	2.44	0.7	1.5	1.05	1.88
Mean difference from placebo†	--	0.66	0.55	--	0.8	--	0.83
95% Confidence Interval	--	(0.25, 1.07)	(0.14, 0.95)	--	(0.4, 1.3)	--	(0.41, 1.25)
p-value	--	0.001*	0.008*	--	<0.001*	--	<0.001*

† Least squares mean adjusted for baseline, gender and geographical region.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.

‡ Not statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.
FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Mirabegron 50 mg once daily was effective at the first measured time point of week 4, and efficacy was maintained throughout the 12-week treatment period. A randomized, active controlled, long term study demonstrated that efficacy was maintained throughout a 1-year treatment period.

Subjective improvement in health-related quality of life measurements
In the three 12-week phase 3 double blind, placebo controlled studies, treatment of the symptoms of OAB with mirabegron once daily resulted in a statistically significant improvement over placebo on the following health-related quality of life measures: treatment satisfaction and symptom bother.

Efficacy in patients with or without prior OAB antimuscarinic therapy
Efficacy was demonstrated in patients with and without prior OAB antimuscarinic therapy. In addition mirabegron showed efficacy in patients who previously discontinued OAB antimuscarinic therapy due to insufficient effect (see Table 4).

Table 4: Co-primary efficacy endpoints for patients with prior OAB antimuscarinic therapy

Parameter	**Pooled studies (046, 047, 074)**		**Study 046**			
	Placebo	**Mirabegron 50 mg**		**Placebo**	**Mirabegron 50 mg**	**Tolterodine ER 4 mg**
Patients with prior OAB antimuscarinic therapy						
Mean number of incontinence episodes per 24 hours (FAS-I)						
n	518	506		167	164	160
Mean baseline	2.93	2.98		2.97	3.31	2.86
Mean change from baseline†	-0.92	-1.49		-1.00	-1.48	-1.10
Mean difference from placebo†	--	-0.57		--	-0.48	-0.10
95% Confidence Interval	--	(-0.81, -0.33)		--	(-0.90, -0.06)	(-0.52, 0.32)
Mean number of micturitions per 24 hours (FAS)						
n	704	688		238	240	231
Mean baseline	11.53	11.78		11.90	11.85	11.76
Mean change from baseline†	-0.93	-1.67		-1.06	-1.74	-1.26
Mean difference from placebo†	--	-0.74		--	-0.68	-0.20
95% Confidence Interval	--	(-1.01, -0.47)		--	(-1.12, -0.25)	(-0.64, 0.23)
Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect						
Mean number of incontinence episodes per 24 hours (FAS-I)						
n	336	335		112	105	102
Mean baseline	3.03	2.94		3.15	3.50	2.63
Mean change from baseline†	-0.86	-1.56		-0.87	-1.63	-0.93
Mean difference from placebo†	--	-0.70		--	-0.76	-0.06
95% Confidence Interval	--	(-1.01, -0.38)		--	(-1.32, -0.19)	(-0.63, 0.50)
Mean number of micturitions per 24 hours (FAS)						
n	466	464		159	160	155
Mean baseline	11.60	11.67		11.89	11.49	11.99
Mean change from baseline†	-0.86	-1.54		-1.03	-1.62	-1.11
Mean difference from placebo†	--	-0.67		--	-0.59	-0.08
95% Confidence Interval	--	(-0.99, -0.36)		--	(-1.15, -0.04)	(-0.64, 0.47)

Pooled studies consisted of 046 (Europe/Australia), 047 (North America [NA]) and 074 (Europe/NA).

† Least squares mean adjusted for baseline, gender, study, subgroup, and subgroup by treatment interaction for Pooled Studies and least squares mean adjusted for baseline, gender, geographical region, subgroup, and subgroup by treatment interaction for Study 046.
FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.
FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with the reference medicinal product containing mirabegron in one or more subsets of the paediatric population in "Treatment of idiopathic overactive bladder" and "Treatment of neurogenic detrusor overactivity" (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (C_{max}) between 3 and 4 hours. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increased more than dose proportionally over the dose range. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of food on absorption
Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered with or without food and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose.

Distribution
Mirabegron is extensively distributed. The volume of distribution at steady state (V_{ss}) is approximately 1 670 L. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. *In vitro* erythrocyte concentrations of ^{14}C-mirabegron were about 2-fold higher than in plasma.

Biotransformation
Mirabegron is metabolised via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of ^{14}C-mirabegron. Two major metabolites were observed in human plasma; both are phase 2 glucuronides representing 16% and 11% of total exposure. These metabolites are not pharmacologically active.

Based on *in vitro* studies, mirabegron is unlikely to inhibit the metabolism of co-administered medicinal products metabolised by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

Although *in vitro* studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination. *In vitro* and *ex vivo* studies have shown the involvement from butyrylcholinesterase, UGT and possibly alcohol dehydrogenase (ADH) in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

CYP2D6 polymorphism
In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean C_{max} and AUC_{inf} of a single 160 mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolisers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Elimination

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CLR) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron to healthy volunteers, approximately 55% of the radiolabel was recovered in the urine and 34% in the faeces. Unchanged mirabegron accounted for 45% of the urinary radioactivity, indicating the presence of metabolites. Unchanged mirabegron accounted for the majority of the faecal radioactivity.

Age

The C_{max} and AUC of mirabegron and its metabolites following multiple oral doses in elderly volunteers (≥65 years) were similar to those in younger volunteers (18 - 45 years).

Gender

The C_{max} and AUC are approximately 40% to 50% higher in females than in males. Gender differences in C_{max} and AUC are attributed to differences in body weight and bioavailability.

Race

The pharmacokinetics of mirabegron are not influenced by race.

Renal impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR-MDRD 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with end stage renal disease (GFR <15 mL/min/1.73 m^2 or patients requiring haemodialysis).

Hepatic impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

5.3 Preclinical safety data

Pre-clinical studies have identified target organs of toxicity that are consistent with clinical observations. Transient increases in liver enzymes and hepatocyte changes (necrosis and decrease in glycogen particles) were seen in rats. An increase in heart rate was observed in rats, rabbits, dogs and monkeys. Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential *in vivo*.

No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryofetal development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36-fold higher than observed at the MHRD. In addition, malformations of the lung (absent accessory lobe of the lung) and increased post-implantation loss were observed in the rabbit at systemic exposures 14-fold higher than observed at the MHRD, while in the rat reversible effects on ossification were noted (wavy ribs, delayed ossification, decreased number of ossified sternebrae, metacarpi or metatarsi) at systemic exposures 22-fold higher than observed at the MHRD. The observed embryofetal toxicity occurred at doses associated with maternal toxicity. The cardiovascular malformations observed in the rabbit were shown to be mediated via activation of the beta 1-adrenoceptor.

Pharmacokinetic studies performed with radio-labelled mirabegron have shown that the parent compound and/or its metabolites are excreted in the milk of rats at levels that were approximately 1.7-fold higher than plasma levels at 4 hours post administration (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Macrogol 2 000 000
Cellulose, microcrystalline (E460)
Hypromellose type 2 208, K100 (E464)
Hydroxypropylcellulose
Butylhydroxytoluene
Magnesium stearate (E572)
Silica, colloidal anhydrous

Film coating
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-OPA/Alu/PVC blisters

Pack sizes:
10, 30, 50, 90, 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
T/A IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road, Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0436/059/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th August 2024