

Summary of Product Characteristics

1. Name of the medicinal product

Nuflex Plus 25/5 mg film-coated tablets.

2. Qualitative and quantitative composition

Each tablet contains 25 mg of mirabegron and 5 mg of solifenacin succinate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Sustained release/Immediate release bilayer 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

The recommended starting doses for combination treatment are Mirabegron is 25 mg once daily and Solifenacin succinate 5 mg once daily.

Method of administration

The tablet is to be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed. It may be taken with or without food.

4.3 Contraindications

MIRABEGRON Hypersensitivity to the active substance(s) or to any of the excipients.

Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg.

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Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.

- Patients hypersensitive to the active substance or to any of the excipients listed in 6.1.
- Patients undergoing haemodialysis.
- Patients with severe hepatic impairment.
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole

4.4 Special warnings and precautions for use

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Renal impairment

Nuflex Plus has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² 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 m²); based on a pharmacokinetic study a dose reduction to 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 m²) concomitantly receiving strong CYP3A inhibitors.

Hepatic impairment

Nuflex Plus 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 .

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 $\geq$ 160 mm Hg or diastolic blood pressure $\geq$ 100 mm Hg).

Patients with congenital or acquired QT prolongation

Nuflex Plus, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. 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 antimuscarinics 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 Nuflex Plus; however, Nuflex Plus should be administered with caution to patients with clinically significant BOO. Nuflex Plus should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

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Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Vesicare. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Vesicare should be used with caution in patients with:

- clinically significant bladder outflow obstruction at risk of urinary retention.
- gastrointestinal obstructive disorders.
- risk of decreased gastrointestinal motility.
- severe renal impairment, and doses should not exceed 5 mg for these patients.
- moderate hepatic impairment, and doses should not exceed 5 mg for these patients.
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole.
- hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- autonomic neuropathy.

QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Angioedema with airway obstruction has been reported in some patients on solifenacin succinate. If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

The maximum effect of Vesicare can be determined after 4 weeks at the earliest.

4.5 Interaction with other medicinal products and other forms of interaction

MIRABEGRON

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 time-dependent 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 Nuflex Plus 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 m²) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food. Nuflex Plus is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors.

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. 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 Nuflex Plus 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.

SOLIFENACIN SUCCINATE Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives

Intake of Vesicare showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel). *Warfarin*

Intake of Vesicare did not alter the pharmacokinetics of *R*-warfarin or *S*-warfarin or their effect on prothrombin time.

Digoxin

Intake of Vesicare showed no effect on the pharmacokinetics of digoxin.

4.6 Fertility, pregnancy, and lactation

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Woman of childbearing potential

Nuflex Plus is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are limited amount of data from the use of Nuflex Plus in pregnant women. Studies in animals have shown reproductive toxicity. 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. 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.

Nuflex Plus should not be administered during breast-feeding. Fertility

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

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Pregnancy

No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice. The use of Vesicare should therefore be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

Nuflex Plus has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

MIRABEGRON

Summary of the safety profile

The safety of Nuflex Plus was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Nuflex Plus 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 Nuflex Plus 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 Nuflex Plus 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Nuflex Plus 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Nuflex Plus 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Nuflex Plus 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	Leukocyt oclastic vasculitis Purpura Angioede ma*		
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.

SOLIFENACIN SUCCINATE

Tabulated list of adverse reactions

MedDRA system organ class	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1000, <1/100	Rare ≥ 1/10000, <1/1000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Infections and infestations			Urinary tract infection Cystitis			
Immune system disorders						Anaphylactic reaction*
Metabolism and nutrition disorders						Decreased appetite* Hyperkalaemia*
Psychiatric disorders					Hallucinations* Confusional state*	Delirium*
Nervous system disorders			Somnolence Dysgeusia	Dizziness*, Headache*		

Eye disorders		Blurred vision	Dry eyes			Glaucoma*
Cardiac disorders						Torsade de Pointes* Electrocardiogram QT prolonged* Atrial fibrillation* Palpitations* Tachycardia*
Respiratory, thoracic and mediastinal disorders			Nasal dryness			Dysphonia*
Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastrooesophageal reflux diseases Dry throat	Colonic obstruction Faecal impaction, Vomiting*		Ileus* Abdominal discomfort*
Hepatobiliary disorders						Liver disorder* Liver function test abnormal*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus*, Rash*	Erythema multiforme*, Urticaria*, Angioedema*	Exfoliative dermatitis*
Musculoskeletal and connective tissue disorders						Muscular weakness*
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment*
General disorders and administration site conditions			Fatigue Peripheral oedema			

4.9 Overdose

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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.

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Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. The highest dose of solifenacin succinate accidentally given to a single patient was 280 mg in a 5 hour period, resulting in mental status changes not requiring hospitalization.

Treatment

In the event of overdose with solifenacin succinate the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour, but vomiting should not be induced.

As for other anticholinergics, symptoms can be treated as follows:

- Severe central anticholinergic effects such as hallucinations or pronounced excitation: treat with physostigmine or carbachol.
- Convulsions or pronounced excitation: treat with benzodiazepines.
- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with beta-blockers.
- Urinary retention: treat with catheterisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

5. Pharmacological properties

5.1 Pharmacodynamic properties

MIRABEGRON

Pharmacotherapeutic group: Urologicals, urinary antispasmodics 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 3adrenoceptor 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

Nuflex Plus 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

Nuflex Plus 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 Nuflex Plus 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 Nuflex Plus on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of mirabegron 100 mg was noninferior 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 Nuflex Plus 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	--	-0.09	-0.07	--	-0.11	--	-0.14

from placebo†							
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.

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 Nuflex Plus in one or more subsets of the paediatric population in “Treatment of idiopathic overactive bladder” and “Treatment of neurogenic detrusor overactivity”.

SOLIFENACIN SUCCINATE Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D08.

Mechanism of action

Solifenacin is a competitive, specific cholinergic-receptor antagonist.

The urinary bladder is innervated by parasympathetic cholinergic nerves.

Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. In vitro and in vivo pharmacological

studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

Pharmacodynamic effects

Treatment with Vesicare in doses of 5 mg and 10 mg daily was studied in several double blind, randomised, controlled clinical trials in men and women with overactive bladder.

As shown in the table below, both the 5 mg and 10 mg doses of Vesicare produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilises over a period of 12 weeks. A long-term open label study demonstrated that efficacy was maintained for at least 12 months. After 12 weeks of treatment approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day. Treatment of the symptoms of overactive bladder also results in a benefit on a number of Quality of Life measures, such as general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

5.2 Pharmacokinetic properties

MIRABEGRON

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 6.5fold. 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 1670 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 Nuflex Plus in volunteers with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m²), 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 m²), 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 m²), 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 m² or patients requiring haemodialysis).

Hepatic impairment

Following single dose administration of 100 mg Nuflex Plus 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).

SOLIFENACIN SUCCINATE Absorption

After intake of Vesicare tablets, maximum solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours. The t_{max} is independent of the dose. The C_{max} and area under the curve (AUC) increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%.

Food intake does not affect the C_{max} and AUC of solifenacin.

Distribution

The apparent volume of distribution of solifenacin following intravenous administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α₁-acid glycoprotein.

Biotransformation

Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin is about 9.5 L/h and the terminal half life of solifenacin is 45 - 68 hours. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Elimination

After a single administration of 10 mg [¹⁴C-labelled]-solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance;

about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

5.3 Preclinical safety data

MIRABEGRON

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 embryofoetal 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, metacarpal or metatarsal) at systemic exposures 22-fold higher than observed at the MHRD. The observed embryofoetal 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.

SOLIFENACIN SUCCINATE

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofoetal development, genotoxicity, and carcinogenic potential. In the pre- and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dose-dependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels. Dose related increased mortality without preceding clinical signs occurred in juvenile mice treated from day 10 or 21 after birth with doses that achieved a pharmacological effect and both groups had higher mortality compared to adult mice. In juvenile mice treated from postnatal day 10, plasma exposure was higher than in adult mice; from postnatal day 21 onwards, the systemic exposure was comparable to adult mice. The clinical implications of the increased mortality in juvenile mice are not known.

6. Pharmaceutical particulars

6.1 List of excipients

Core tablet

Polyox WSR N60K NF

Macrogol 6000 BP

Hydroxypropyl cellulose BP

Magnesium stearate BP

Microcrystalline cellulose USP

Calcium hydrogen Phosphate BP

Brilliant blue water soluble IH

Croscarmellose sodium BP

Seal Coating

Tabcoat TC

Film coating

Opadry QX

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product stored below 30°C.

6.5 Nature and contents of container

Alu -Alu blisters in cartons containing 30 tablets.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

Cosmos Limited

Near Rangwe close, off lunga lunga road

PO bx 41433-00100

Nairobi, Kenya

8. Marketing Authorization Number

H2025/CTD12391/26147

9. Date of first authorization/renewal of the authorization

08/07/2025

10. Date of revision of the text

08/07/2025