

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Nuflex 50 mg film coated tablets.

1. Qualitative and quantitative composition

Nuflex 50 mg sustained-release film coated tablets

Each tablet contains 50 mg of mirabegron.

For the full list of excipients, see section 6.1.

2. Pharmaceutical form

Sustained release film coated tablet.

3. Clinical particulars

3.1 Therapeutic indications

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

3.2 Posology and method of administration

Posology

Adults (including elderly patients)

The recommended dose is 50 mg once daily

Special populations

Renal and hepatic impairment

Nuflex has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors.

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

		ng CYP3A inhibitors ⁽³⁾	
		out inhibitor	a inhibitor
al impairment ⁽¹⁾		ng	ng
	erate	ng	ng
	re	ng	recommended
atic impairment ⁽²⁾		ng	ng
	erate	ng	recommended

Mild: GFR 60 to 89 mL/min/1.73 m²; moderate: GFR 30 to 59 mL/min/1.73 m²; severe: GFR 15 to 29 mL/min/1.73 m².

1. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
2. Strong CYP3A inhibitors

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. It may be taken with or without food.

3.3 Contraindications

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

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

3.4 Special warnings and precautions for use

Renal impairment

Nuflex 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 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, 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; however, Nuflex should be administered with caution to patients with clinically significant BOO. Nuflex should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

3.5 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 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 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 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 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.

3.6 Fertility, pregnancy and lactation

Woman of childbearing potential

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

Pregnancy

There are limited amount of data from the use of Nuflex 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 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.

3.7 Effects on ability to drive and use machines

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

3.8 Undesirable effects

Summary of the safety profile

The safety of Nuflex 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 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 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 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Nuflex 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Nuflex 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Nuflex 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.

ADRA System organ class	Very common	Common	Uncommon	Rare	Very rare Not known (cannot be estimated from the available data)
Infections and infestations	Urinary tract infection	Urinary tract infection			
Cardiac disorders					Arrhythmia* Atrial fibrillation*
Respiratory system disorders	Dyspnoea* Cough*				
Other disorders			Peripheral oedema		

Cardiac disorders	Myocardia	Arrhythmia Atrial fibrillation			
Respiratory disorders				Hypertensive crises*	
Gastrointestinal disorders	Nausea* Constipation*Diarrhoea*	Dyspepsia Gastritis	Angioedema		
Skin and subcutaneous disorders		Acne Erythema Macular PapularPruritus	Exfoliative dermatitis Erythema multiforme Angioedema*		
Musculoskeletal and connective tissue disorders		Joint swelling			
Renal and urinary disorders			Urinary retention*		
Reproductive system and disorders		Vaginal discharge			
Investigations		Blood pressure decreased Creatinine increased Alanine aminotransferase increasedALT decreased			

*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 Pharmacovigilance Electronic Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org/>

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.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

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 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

Nuflex 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 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 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 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 Nuflex 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

ometer	ed studies , 047, 074)	
	ebo	abegron ng
n number of incontinence episodes per 24 hours (FAS-I) (Co-primary)		

n baseline		
n change from baseline†	0	9
n difference from placebo† (95% CI)		0 (-0.58, -0.21)
lue		001#
n number of micturitions per 24 hours (FAS) (Co-primary)		
	8	4
n baseline	8	0
n change from baseline†	0	5
n difference from placebo† (95% CI)		5 (-0.75, -0.36)
lue		001#
n volume voided (mL) per micturition (FAS) (Secondary)		

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	Day 046			Day 047		Day 074	
	Placebo	Abegron 50 mg	Terodiline ER 4 mg	Placebo	Abegron 50 mg	Placebo	Abegron 50 mg
Number of incontinence episodes per 24 hours (FAS-I) (Co-primary)							
Mean baseline							
Mean change from baseline†	7	7	7	8	7	6	8
Mean difference from placebo†		-1	0		-1		-2
Confidence Interval		(-2, -0.09)	(-2, 0.21)		(-6, -0.03)		(-6, -0.08)
P-value		0.3#			0.6#		0.1#
Number of micturitions per 24 hours (FAS) (Co-primary)							
Mean baseline	11	5	5	11	10	8	6
Mean change from baseline†	4	3	9	5	6	3	9
Mean difference from placebo†		0	5		-1		-2
Confidence Interval		(-10, -0.29)	(-5, 0.06)		(-8, -0.24)		(-6, -0.08)
P-value		0.001#			0.1#		0.05#
Mean volume voided (mL) per micturition (FAS) (Secondary)							
Mean baseline	7	11	6	5	3	10	3
Mean change from baseline†							
Mean difference from placebo†							
Confidence Interval		(-17.4)	(-18.2)		(-17.9)		(-18.6)
P-value		0.001#	0.001*		0.1#		0.001#

n level of urgency (FAS) (Secondary)

† 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.

Nuflex 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	Phase 3 studies (N = 047, 074)		Phase 4 study 046		
	Placebo	Mirabegron 50mg	Placebo	Mirabegron 50mg	Trospirine ER4 mg

ents with prior OAB antimuscarinic therapy					
n number of incontinence episodes per 24 hours (FAS-I)					
n baseline					
n change from baseline†	2	0	0	3	0
n difference from placebo†		7		3	0
Confidence Interval		1, -0.33)		0, -0.06)	2, 0.32)
n number of micturitions per 24 hours (FAS)					
n baseline	3	3	0	5	6
n change from baseline†	3	7	5	4	5
n difference from placebo†		4		3	0
Confidence Interval		1, -0.47)		2, -0.25)	4, 0.23)
ents with prior OAB antimuscarinic therapy who discontinued due to insufficient effect					
n number of incontinence episodes per 24 hours (FAS-I)					
n baseline					
n change from baseline†	5	5	7	3	3
n difference from placebo†		0		5	5
Confidence Interval		1, -0.38)		2, -0.19)	3, 0.50)
n number of micturitions per 24 hours (FAS)					
n baseline	0	7	9	9	9
n change from baseline†	5	4	3	2	-
n difference from placebo†		7		9	3
Confidence Interval		9, -0.36)		5, -0.04)	4, 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 in one or more subsets of the paediatric population in “Treatment of idiopathic overactive bladder” and “Treatment of neurogenic detrusor overactivity”.

5.3 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 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 (CL_R) 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 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 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).

5.4 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 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, metacarpi or metatarsi) 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.

6.0 Pharmaceutical particulars

6.1 List of excipients

Core tablet

Polyox WSR N60K NF

Microcrystaine cellulose

Butylhydroxytoluene

Polyox WSR1105 NF

Sodium stearyl fumarate

Film coating

Opadry II yellow

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.

6.7 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

H2024/CTD11161/24624

9. Date of registration/renewal of registration

08/01/2024

10. Date of revision of the text

22/08/2026

