

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIRABA-S

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film tablet contains: Mirabegron 25mg & Solifenacin succinate 5 mg Tablets

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A Yellow colored round shape biconvex, film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Overactive bladder in adults

Mirabegron Astellas prolonged-release tablets are indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Neurogenic detrusor overactivity in the paediatric population

Mirabegron Astellas prolonged-release tablets are indicated for treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years.

Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

4.2 Posology and method of administration

Posology

Overactive bladder

Adults (including elderly patients)

The recommended dose is 50 mg once daily.

Neurogenic detrusor overactivity in the paediatric population

Paediatric patients 3 to less than 18 years of age with NDO may be administered Mirabegron Astellas prolonged-release tablets or Mirabegron Astellas granules for prolonged-release oral suspension based on the body weight of the patient. The prolonged-release tablets may be administered to patients weighing 35 kg or more; the

granules for prolonged-release oral suspension are recommended for patients below 35 kg. Patients administered 6 ml oral suspension dose may be switched to 25 mg tablet dose and patients administered 10 ml oral suspension dose may be switched to 50 mg tablet dose.

The recommended starting dose of Mirabegron Astellas prolonged-release tablets is 25 mg once daily with food. If needed, the dose may be increased to a maximum dose of 50 mg once daily with food after 4 to 8 weeks. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated.

Missed dose

Patients should be instructed to take any missed doses, unless more than 12 hours have passed since the missed dose. If more than 12 hours have passed, the missed dose can be skipped, and the next dose should be taken at the usual time.

Special populations

Renal and hepatic impairment

Mirabegron Astellas has not been studied in patients with end stage renal disease (ESRD) (estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m²), patients requiring haemodialysis, or patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for adult OAB patients with renal or hepatic impairment (see sections 4.4, 4.5 and 5.2).

Table 1: Daily dosing recommendations for adult OAB patients with renal or hepatic impairment

Parameter	Classification	Dose (mg)
Renal impairment ⁽¹⁾	Mild/Moderate*	50
	Severe**	25
	ESRD	Not recommended
Hepatic impairment ⁽²⁾	Mild*	50
	Moderate**	25
	Severe	Not recommended

1. Mild/Moderate: eGFR 30 to 89 ml/min/1.73 m²; Severe: eGFR 15 to 29 ml/min/1.73 m²; ESRD: eGFR < 15 ml/min/1.73 m².

2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B; Severe: Child-Pugh Class C.

* In patients with mild to moderate renal impairment or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors, the recommended dose is no more than 25 mg.

** Not recommended for use in patients with severe renal impairment or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors.

The following table provides the daily dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment weighing 35 kg or more (see sections 4.4 and 5.2).

Table 2: Daily dosing recommendations for paediatric NDO patients aged 3 to less than 18 years with renal or hepatic impairment weighing 35 kg or more

Parameter	Classification	Starting dose (mg)	Maximum dose (mg)
Renal impairment ⁽¹⁾	Mild/Moderate*	25	50
	Severe**	25	25
	ESRD	Not recommended	
Hepatic impairment ⁽²⁾	Mild*	25	50
	Moderate**	25	25
	Severe	Not recommended	

1. Mild/Moderate: eGFR 30 to 89 ml/min/1.73 m²; Severe: eGFR 15 to 29 ml/min/1.73 m²;

ESRD: eGFR < 15 ml/min/1.73 m². No dose adjustment is necessary for patients with mild to moderate renal impairment.

2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B; Severe: Child-Pugh Class C.

* In patients with mild to moderate renal impairment or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors, the recommended dose is no more than the starting dose.

** Not recommended for use in patients with severe renal impairment or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors.

Gender

No dose adjustment is necessary according to gender.

Paediatric population

Overactive bladder

The safety and efficacy of mirabegron in children below 18 years of age with OAB have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Neurogenic detrusor overactivity

The safety and efficacy of mirabegron in children below 3 years of age have not yet been established.

Adults, including the elderly

The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may be increased to 10 mg solifenacin succinate once daily.

Paediatric population

The safety and efficacy of solifenacin in children have not yet been established. Therefore, solifenacin should not be used in children.

Patients with renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min). Patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) should be treated with caution and receive no more than 5 mg once daily (see section 5.2).

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) should be treated with caution and receive no more than 5 mg once daily (see section 5.2).

Potent inhibitors of cytochrome P450 3A4

The maximum dose of solifenacin tablets should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors e.g. ritonavir, nelfinavir, itraconazole (see section 4.5).

Method of administration

Overactive bladder in adults

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.

Neurogenic detrusor overactivity in the paediatric population

The tablet is to be taken with liquids, swallowed whole, and is not to be chewed, divided, or crushed. It should be taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance(s) 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.
- Urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.

- Undergoing haemodialysis (see section 5.2).
- Severe hepatic impairment (see section 5.2).
- Severe renal impairment or moderate hepatic impairment and treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole (see section 4.5).

4.4 Special warnings and precautions for use

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Renal impairment

Mirabegron has not been studied in patients with ESRD (eGFR < 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 (eGFR 15 to 29 ml/min/1.73 m²); based on a pharmacokinetic study (see section 5.2) a dose of 25 mg once daily is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m²) 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

Overactive bladder in adults

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).

Neurogenic detrusor overactivity in the paediatric population

Mirabegron can increase blood pressure in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

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 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 post-marketing 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. Mirabegron 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 solifenacin. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solifenacin 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 (creatinine clearance ≤ 30 ml/min; see sections 4.2 and 5.2) and doses should not exceed 5 mg for these patients.
- Moderate hepatic impairment (Child-Pugh score of 7 to 9; see sections 4.2 and 5.2) and doses should not exceed 5 mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see sections 4.2 and 4.5).
- Hiatus hernia/gastroesophageal 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Angioedema with airway obstruction has been reported in some patients on solifenacin. If angioedema occurs, solifenacin 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 solifenacin 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 mirabegron is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (eGFR 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 (see section 4.2). Mirabegron is not recommended in patients with severe renal impairment (eGFR 15 to 29 ml/min/1.73 m²) 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 mirabegron 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.

Paediatric population

Interaction studies have only been performed in adults.

SOLIFENACIN

Pharmacological interactions

Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with solifenacin before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

In vitro studies have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin

Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of solifenacin should be restricted to 5 mg when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (see section 4.2). Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contraindicated in patients with severe renal impairment or moderate hepatic impairment.

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been studied as well as the effect of higher affinity CYP3A4 substrates on solifenacin exposure. Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with higher affinity (e.g. verapamil, diltiazem) and CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine).

Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives

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

Warfarin

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

Digoxin

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no or limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Mirabegron Astellas 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 Astellas should not be used 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

Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue (see section 4.8), the ability to drive and use machines may be negatively affected.

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

4.8 Undesirable effects

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Summary of the safety profile

The safety of mirabegron was evaluated in 8 433 adult 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 adult 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 adults with OAB 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		
Hepatobiliary disorders		GGT increased AST increased ALT increased			
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular	Leukocytoclastic vasculitis Purpura Angioedema*		

		Pruritus			
Musculoskeletal and connective tissue disorders		Joint swelling			
Renal and urinary disorders			Urinary retention*		
Reproductive system and breast disorders		Vulvovaginal pruritus			
Investigations		Blood pressure increased			

*observed during post-marketing experience

Paediatric population

The safety of mirabegron tablets and oral suspension was evaluated in 86 paediatric patients aged 3 to less than 18 years with neurogenic detrusor overactivity in a 52-week, open-label, baseline-controlled, multicentre, dose titration study. The most commonly reported adverse reactions observed in the paediatric population were urinary tract infection, constipation, and nausea.

In the paediatric patients with NDO, no severe adverse reactions were reported.

The safety of mirabegron tablets and oral suspension was evaluated in 26 paediatric patients aged 5 to less than 18 years of age with overactive bladder in a 12-week, double-blind, randomised, multicentre, parallel group, placebo-controlled sequential dose titration study. The most commonly reported adverse reactions observed in the paediatric population were nasopharyngitis, fatigue and mood swing.

Overall, the safety profile in children and adolescents is similar to that observed in adults.

SOLIFENACIN

Summary of the safety profile

Due to the pharmacological effect of solifenacin, it may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergic undesirable effects is dose related.

The most commonly reported adverse reaction with solifenacin was dry mouth. It occurred in 11% of patients treated with 5 mg once daily, in 22% of patients treated with 10 mg once daily and in 4% of placebo-treated patients. The severity of dry mouth was generally mild and only occasionally led to discontinuation of treatment. In general, medicinal product compliance was very high (approximately 99%) and approximately 90% of the patients treated with solifenacin completed the full study period of 12 weeks treatment.

Tabulated list of adverse reactions

MedDRA system organ	Very common	Common ≥ 1/100,	Uncommon ≥ 1/1,000,	Rare ≥	Very rare <1/10,000	Not known (cannot be
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class	≥ 1/10	<1/10	<1/100	1/10,000, <1/1,000		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	Gastro-oesophageal reflux disease 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			

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 the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Mirabegron has been administered to healthy adult 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 adult volunteers.

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

Symptoms

Overdose 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 hospitalisation.

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 a dark room.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with known risk for QT-prolongation (i.e. hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing

cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

MIRABEGRON

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 adult 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.

Effects on blood pressure in paediatric patients with NDO

Mirabegron can increase blood pressure in paediatric patients. Blood pressure increases may be larger in children (3 to less than 12 years of age) than in adolescents (12 to less than 18 years of age). Blood pressure should be measured at baseline and periodically during treatment with mirabegron.

Effect on intraocular pressure (IOP)

Mirabegron 100 mg once daily did not increase IOP in healthy adult 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

Overactive bladder in adult patients

Efficacy of mirabegron was evaluated in three phase 3 randomised, 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 3 and 4).

Table 3: Co-primary and selected secondary efficacy endpoints at end of treatment for pooled studies in adults

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	1 328	1 324
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	1 328	1 322
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	1 325	1 323
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	1 324	1 320
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	1 195	1 189
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 randomised 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 4: Co-primary and selected secondary efficacy endpoints at end of treatment for studies 046, 047 and 074 in adults

Param eter	Study 046			Study 047		Study 074	
	Plac ebo	Mirabe gron 50 mg	Toltero dine ER 4 mg	Plac ebo	Mirabe gron 50 mg	Plac ebo	Mirabe gron 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 micturations 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

e							
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	1.89	2.55	2.44	0.7	1.5	1.05	1.88

baseline*							
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 randomised 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 randomised, 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 5).

Table 5: Co-primary efficacy endpoints for adult 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	--	-0.70	--	-0.76	-0.06

placebo*					
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 randomised 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.

Neurogenic detrusor overactivity in paediatric patients

Efficacy of mirabegron tablets and oral suspension was evaluated in a 52-week, open-label, baseline-controlled, multicentre, dose titration study for the treatment of NDO in paediatric patients. Patients had a diagnosis of NDO with involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H₂O and performed clean intermittent catheterisation (CIC). Patients ≥ 35 kg received tablets and patients < 35 kg (or ≥ 35 kg but unable to tolerate tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on body weight). The dose titration period was a maximum of 8 weeks followed by a dose maintenance period of at least 52 weeks.

A total of 86 patients aged 3 to less than 18 years of age received mirabegron. Of these, 71 patients completed treatment through week 24 and 70 completed 52 weeks of treatment. A total of 68 patients had valid urodynamic measurements for evaluation of efficacy. The study population included 39 (45.3%) males and 47 (54.7%) females. The optimised maintenance dose within this study population included 94% of patients at the maximum dose, and 6% of patients at the starting dose.

The most common (in greater than 10% of all patients) background medical conditions related to NDO in children and adolescents included in the study were congenital central nervous system anomaly (54.5% and 48.4%, respectively), meningomyelocele (27.3% and 19.4%, respectively), and spina bifida (10.9% and 12.9%, respectively). In adolescents, 12.9% had a spinal cord injury.

The primary efficacy endpoint was change from baseline in maximum cystometric capacity (MCC) after 24 weeks of mirabegron treatment. Improvements in MCC were observed in all patient groups (see Table 6).

Table 6: Primary efficacy endpoint in paediatric patients with NDO

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
Maximum cystometric capacity (ml)		
Baseline	158.6 (94.5)	238.9 (99.1)
Week 24	230.7 (129.1)	352.1 (125.2)
Change from baseline	72.0 (87.0)	113.2 (82.9)
95% Confidence Interval	(45.2, 98.8)	(78.9, 147.4)

* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

The secondary efficacy endpoints were change from baseline in bladder compliance, number of overactive detrusor contractions, detrusor pressure at end of bladder-filling, bladder volume prior to first detrusor contraction, maximum catheterised urine volume per day, and number of leakage episodes per day after 24 weeks of mirabegron treatment (see Table 7).

Table 7: Secondary efficacy endpoints in paediatric patients with NDO

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
Bladder compliance (ml/cm H₂O)†		
Baseline	14.5 (50.7)	11.0 (10.0)
Week 24	29.6 (52.8)	23.8 (15.3)
Change from baseline	14.6 (42.0)	13.5 (15.0)
95% Confidence Interval	(-0.3, 29.5)	(6.7, 20.4)
Number of overactive detrusor contractions (> 15 cm H₂O)†		
Baseline	3.0 (3.8)	2.0 (2.9)
Week 24	1.0 (2.2)	1.4 (2.3)
Change from baseline	-1.8 (4.1)	-0.7 (3.8)
95% Confidence Interval	(-3.2, -0.4)	(-2.4, 0.9)
Detrusor pressure (cm H₂O) at end of bladder-filling†		
Baseline	42.2 (26.2)	38.6 (17.9)
Week 24	25.6 (21.2)	27.8 (27.8)
Change from baseline	-18.1 (19.9)	-13.1 (19.9)

95% Confidence Interval	(-24.8, -11.3)	(-22.0, -4.3)
Bladder volume prior to first detrusor contraction (> 15 cm H₂O)†		
Baseline	115.8 (87.0)	185.2 (121.2)
Week 24	207.9 (97.8)	298.7 (144.4)
Change from baseline	93.1 (88.1)	121.3 (159.8)
95% Confidence Interval	(64.1, 122.1)	(53.8, 188.8)
Maximum catheterised urine volume per day (ml)†		
Baseline	300.1 (105.7)	367.5 (119.0)
Week 24	345.9 (84.6)	449.9 (146.6)
Change from baseline	44.2 (98.3)	81.3 (117.7)
95% Confidence Interval	(13.2, 75.2)	(30.4, 132.3)
Number of leakage episodes per day†		
Baseline	3.2 (3.7)	1.8 (1.7)
Week 24	0.7 (1.2)	0.9 (1.2)
Change from baseline	-2.0 (3.2)	-1.0 (1.1)
95% Confidence Interval	(-3.2, -0.7)	(-1.5, -0.5)

* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24; Bladder compliance: n=33/21; Number of overactive detrusor contractions: n=36/22; Detrusor pressure at end of bladder-filling: n=36/22; Bladder volume prior to first detrusor contraction: n=38/24; Maximum catheterised urine volume per day: n=41/23; Number of leakage episodes per day: n=26/21.

Patient- or clinician-reported questionnaire endpoints included acceptability, change from baseline in the Pediatric Incontinence Questionnaire (PIN-Q), change from baseline in the Patient Global Impression of Severity Scale (PGI-S), and Clinician Global Impression of Change (CGI-C) (see Table 8).

Table 8: Patient- or clinician-reported questionnaire endpoints in paediatric patients with NDO

Parameter	Children aged 3 to < 12 years (N=43)* Mean (SD)	Adolescents aged 12 to < 18 years (N=25)* Mean (SD)
Pediatric Incontinence Questionnaire (PIN-Q) score†		
Baseline	30.8 (15.7)	29.4 (14.6)
Week 24	30.6 (15.2)	25.2 (15.5)
Change from baseline	2.0 (10.5)	-4.9 (14.1)
95% Confidence Interval	(-2.4, 6.4)	(-11.3, 1.5)
Total Patient Global Impression of Severity Scale (PGI-S) score†		
Baseline	2.2 (0.8)	2.3 (0.9)
Week 24	2.6 (0.8)	3.0 (0.7)
Change from baseline	0.3 (1.2)	0.6 (1.0)
95% Confidence Interval	(-0.1, 0.8)	(0.1, 1.0)
Total Clinician Global Impression of Change (CGI-C) at week 24, N (%)†		

Very Much Improved	6 (14.6%)	10 (41.7%)
Much Improved	24 (58.5%)	7 (29.2%)
Minimally Improved	6 (14.6%)	5 (20.8%)
No Change	4 (9.8%)	1 (4.2%)
Minimally Worse	1 (2.4%)	1 (4.2%)
Much Worse	0	0
Very Much Worse	0	0

* N is the number of patients who took at least one dose and provided valid values for MCC at baseline and week 24.

† Number of patients (children/adolescents) with data available for both baseline and week 24. PIN-Q score: n=24/21, Total PGI-S score: n=25/22; Total CGI-C at week 24: n=41/24.

Paediatric population

Overactive bladder

Efficacy of mirabegron tablets and oral suspension was evaluated in a 12-week, double-blind, randomised, multicentre, parallel group, placebo-controlled sequential dose titration study for the treatment of OAB in paediatric patients (5 to less than 18 years of age). Patients ≥ 35 kg received tablets and patients < 35 kg (or ≥ 35 kg but unable to swallow tablets) received oral suspension. For all patients, mirabegron was administered orally once daily with food. The starting dose was a 25 mg tablet or between 3-6 ml of oral suspension (depending on patient weight). This dose was up-titrated to 50 mg tablet or between 6-11 ml of oral suspension (depending on patient weight). Dose titration to the higher dose was conducted after 4 weeks on treatment, unless the investigator decided otherwise.

A total of 23 children (aged 5 to less than 12 years) and 3 adolescents (aged 12 to less than 18 years of age) received study drug: 13 subjects received placebo and 13 subjects received mirabegron. Ten of the 12 subjects in the placebo group and 9 of 11 subjects in the mirabegron group completed the study through 12 weeks of treatment.

The primary efficacy endpoint was the change from baseline in the mean number of micturations per 24 hours after 12 weeks of treatment and was assessed only in children (aged 5 to less than 12 years).

Due to the small number of subjects, a proper assessment of the efficacy endpoints was not possible, and the observed results were inconclusive.

The adjusted LS mean (SEM) change from baseline to week 12/end of treatment in the frequency of micturition events per 24 hours was -3.84 (0.89) in children on placebo and -1.62 (0.89) in children on mirabegron. The LS mean (SEM) difference between treatment groups (placebo minus mirabegron) was not statistically significant: 2.22 (1.34) (90% CI: -0.15, 4.59; P = 0.121).

The European Medicines Agency has waived the obligation to submit the results of studies with Mirabegron Astellas in all subsets of the paediatric population in "Treatment of idiopathic overactive bladder" (see section 4.2 for information on paediatric use).

SOLIFENACIN

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04BD08.

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 solifenacin 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 solifenacin produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilised 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.

Results (pooled data) of four controlled Phase 3 studies with a treatment duration of 12 weeks

	Placebo	Solifenacin 5 mg o.d.	Solifenacin 10 mg o.d.	Tolterodine 2 mg b.i.d.
No. of micturitions/24 h				
Mean baseline	11.9	12.1	11.9	12.1
Mean reduction from baseline	1.4 (12%)	2.3 (19%)	2.7 (23%)	1.9 (16%)
% change from baseline	1138	552	1158	250
n		<0.001	<0.001	0.004
p-value*				
No. of urgency episodes/24 h				
Mean baseline	6.3	5.9	6.2	5.4
Mean reduction from baseline	2.0 (32%)	2.9 (49%)	3.4 (55%)	2.1 (39%)
% change from baseline	1124	548	1151	250
n		<0.001	<0.001	0.031
p-value*				
No. of incontinence episodes/24 h				
Mean baseline	2.9	2.6	2.9	2.3
Mean reduction from baseline	1.1 (38%)	1.5 (58%)	1.8 (62%)	1.1 (48%)
% change from baseline	781	314	778	157
n		<0.001	<0.001	0.009
p-value*				

n p-value*				
No. of nocturia episodes/24 h				
Mean baseline	1.8	2.0	1.8	1.9
Mean reduction from baseline	0.4 (22%)	0.6 (30%)	0.6 (33%)	0.5 (26%)
% change from baseline	1005	494	1035	232
n p-value*		0.025	<0.001	0.199
Volume voided/micturition				
Mean baseline	166 ml	146 ml	163 ml	147 ml
Mean increase from baseline	9 ml (5%)	32 ml (21%)	43 ml (26%)	24 ml (16%)
% change from baseline	1135	552	1156	250
n p-value*		<0.001	<0.001	<0.001
No. of pads/24 h				
Mean baseline	3.0	2.8	2.7	2.7
Mean reduction from baseline	0.8 (27%)	1.3 (46%)	1.3 (48%)	1.0 (37%)
% change from baseline	238	236	242	250
n p-value*		<0.001	<0.001	0.010

Note: In 4 of the pivotal studies, solifenacin 10 mg and placebo were used. In 2 out of the 4 studies also solifenacin 5 mg was used and one of the studies included tolterodine 2 mg bid.

Not all parameters and treatment groups were evaluated in each individual study. Therefore, the numbers of patients listed may deviate per parameter and treatment group.

* P-value for the pair-wise comparison to placebo

5.2 Pharmacokinetic properties

SOLIFENACIN

General characteristics

Absorption

After intake of solifenacin 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 a 1-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).

Linearity/non-linearity

Pharmacokinetics are linear in the therapeutic dose range.

Special populations

Elderly

No dosage adjustment based on patient age is required. Studies in the elderly have shown that the exposure to solifenacin, expressed as the AUC, after administration of solifenacin succinate (5 mg and 10 mg once daily) was similar in healthy elderly subjects (aged 65 – 80 years) and healthy young subjects (aged less than 55 years). The mean rate of absorption expressed as t_{max} was slightly slower in the elderly and the terminal half-life was approximately 20% longer in elderly subjects. These modest differences were considered not clinically significant.

The pharmacokinetics of solifenacin have not been established in children and adolescents.

Gender

The pharmacokinetics of solifenacin are not influenced by gender.

Race

The pharmacokinetics of solifenacin are not influenced by race.

Renal impairment

The AUC and C_{max} of solifenacin in mild and moderate renally impaired patients was not significantly different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), exposure to solifenacin was significantly

greater than in the controls, with increases in C_{max} of about 30%, AUC of more than 100% and t_{1/2} of more than 60%. A statistically significant relationship was observed between creatinine clearance and solifenacin clearance.

Pharmacokinetics in patients undergoing haemodialysis has not been studied.

Hepatic impairment

In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased by 60% and t_{1/2} doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment has not been studied.

MIRABEGRON

Absorption

Adults

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 adult 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.

Paediatric population

The median T_{max} of mirabegron following oral administration of a single dose of mirabegron tablets or oral suspension in patients under fed state was 4-5 hours. Population pharmacokinetic analysis predicted that the median T_{max} of mirabegron tablets or oral suspension at steady-state was 3-4 hours.

The bioavailability of the oral suspension formulation is lower than that of the tablet. The ratio of the population mean exposure (AUC_{tau}) of the oral suspension to the tablet is approximately 45%.

Effect of food on absorption

Adults

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.

Paediatric population

The population pharmacokinetic model predicted that the patients receiving mirabegron in the fed state would have 44.7% of steady-state AUC_{tau} relative to an equal dose administered in the fasted state. This value is consistent with the AUC_{inf} results seen in the single-dose food effects studies for mirabegron. In the phase 3 paediatric study, mirabegron was administered with food and demonstrated both safety and efficacy. Dosing recommendations are based upon the exposures expected in the fed state. Therefore, in paediatric patients, mirabegron should be taken with food at the recommended dose.

Distribution

Adults

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 ¹⁴C-mirabegron were about 2-fold higher than in plasma.

Paediatric population

Mirabegron volume of distribution was relatively large and increased with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. Age, sex and patient population had no impact on volume of distribution after accounting for potential differences in body weight.

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 ¹⁴C-mirabegron. Two major metabolites were observed in adult 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 adult 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 adult patients who are CYP2D6 poor metabolisers.

Elimination

Adults

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 ¹⁴C-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.

Paediatric population

Mirabegron clearance was predicted to increase in patients with increasing body weight in accordance with allometric principles based on population pharmacokinetic analysis. The apparent clearance parameter was impacted significantly by dose, formulation, and food effects on relative bioavailability. Values of apparent clearance were highly variable but generally similar between children and adolescents, despite body weight differences, because of these effects on bioavailability.

Age

Adults

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).

Paediatric population

In patients 3 to less than 18 years of age, age was not predicted to have any impact on key mirabegron pharmacokinetic parameters after accounting for differences in body weight. Models including age did not result in meaningful improvements to the paediatric population pharmacokinetic model, indicating that inclusion of body weight was sufficient to address differences in mirabegron pharmacokinetics due to age.

Gender

Adults

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.

Paediatric population

Gender has no meaningful impact on mirabegron pharmacokinetics in the paediatric population from 3 to less than 18 years of age.

Race

The pharmacokinetics of mirabegron in adults are not influenced by race.

Renal impairment

Following single dose administration of 100 mg mirabegron in adult 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 adult volunteers with normal renal function. In adult 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 adult 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 ESRD (eGFR < 15 ml/min/1.73 m²) or patients requiring haemodialysis.

Hepatic impairment

Following single dose administration of 100 mg mirabegron in adult volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to adult volunteers with normal hepatic function. In adult 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 and reduced plasma leptin levels were noted. 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.

Mirabegron had no discernible effect on gonadotropic or sex steroid hormone levels. In addition, 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.

The overall safety profile seen in juvenile rats was comparable to that observed in adult animals. Juvenile rats orally administered mirabegron for 13 weeks showed elevated liver enzymes with an increase in liver weights without histopathological findings at systemic exposures approximately 12-fold higher than the projected human systemic exposure in children. Repeat dose safety studies performed in juvenile rats showed no effect on physical development or sexual maturation. Mirabegron administration from weaning through sexual maturation had no effect on mating ability, fertility or embryofoetal development. Mirabegron administration increased lipolysis and food consumption and decreased body weight gain in juvenile rats.

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).

Non-clinical safety data on acetylsalicylic acid and caffeine have not revealed findings which are of relevance to the recommended dosage and use of the product, and which are not already addressed in the clinical data section (See Pregnancy and Lactation). Oral administration of caffeine to rats during the period of organogenesis at a dose that was 2.7 fold greater than the clinical dose was reported to cause a decrease in foetal weight and foetal malformations consisting of club foot, ectrodactyly, cleft palate, and retarded ossification. Similar effects, consisting of significant increases in foetal resorptions and foetal malformations that included cleft palate and digital defects, were reported following intraperitoneal administration of caffeine to mice on days 7 through 14 of gestation at a dose that was 3.4 -fold greater than the clinical dose.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal 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:

- ☐ Microcrystalline cellulose BP
- ☐ Maize starch BP
- ☐ Hypromellose K - 100 M BP
- ☐ Hypromellose K - 15 M BP
- ☐ Ethyl cellulose BP
- ☐ Povidone K - 90 BP
- ☐ Isopropyl alcohol BP

- ☐ Purified Talc BP
- ☐ Magnesium Stearate BP
- ☐ Dichloromethane BP
- ☐ Croscarmellose Sodium BP
- ☐ Crospovidone (Type - B) BP
- ☐ Povidone K - 30 BP
- ☐ Sodium starch glycolate (Type - A) BP
- ☐ Colloidal Anhydrous Silica BP
- ☐ Sodium Lauryl Sulfate BP
- ☐ Yellow Oxide of Iron IH

Film Coat

- ☐ Dr. Coat IH
- ☐ Isopropyl alcohol BP
- ☐ Dichloromethane BP
- ☐ Yellow Oxide of Iron IH
- ☐ Titanium Dioxide BP

6.2 Incompatibilities

Not Known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30° C. Protect from light and moisture

6.5 Nature and contents of container

A Yellow coloured round shape biconvex, film coated tablets. Such 10 tablets are packed in Alu-Alu Blister. Such 1 Alu-Alu blister is packed in a printed carton along with insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Tiba healthcare Ltd.
PO BOX- 243-00623,
Nairobi, Kenya.

Manufactured at –

Salud Care (I) Pvt Ltd

8. MARKETING AUTHORISATION NUMBER(S) –

H2022/CTD10046/22823

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--

APRIL 2023

10. DATE OF REVISION OF THE TEXT

December 2027