**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product

Miraba-S Tablets
Mirabegron (Extended-Release) 25mg & Solifenacin succinate 5 mg Tablets

## 2. Qualitative and quantitative composition

Each film coated tablet contains: Mirabegron (Extended-Release) 25mg & Solifenacin succinate 5 mg

For a full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film coated tablet
A Yellow coloured round shape biconvex, film coated tablet.

## 4. Clinical particulars

### 4.1 Therapeutic indications

MIRABA-S is indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

### 4.2 Posology and method of administration

Based on individual efficacy and tolerability, may increase dose to two tablets daily after 4 to 8 weeks.
Dose Adjustments in Specific Populations:
Patients with Severe Renal Impairment (CLcr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m2) or Patients with Moderate Hepatic Impairment (Child-Pugh Class B): Maximum dose is once daily.
Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment: Not recommended.
Method of administration
Swallowed whole with water, with or without food and do not chewed, divided or crushed.

### 4.3 Contraindications

Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets is contraindicated in patients who have known hypersensitivity reactions to Mirabegron and Solifenacin succinate or any of the ingredients.

### 4.4 Special warnings and precautions for use

Increases in Blood Pressure:

Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients.
Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets is not recommended for use in severe uncontrolled

hypertensive patients.

Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Muscarinic Antagonist Drugs for Overactive Bladder

In patients taking Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets S, urinary retention has been reported to occur in patients with bladder outlet obstruction (BOO) and in patients taking muscarinic antagonist medications for the treatment of OAB. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets patients; however, Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets should still be administered with caution to patients with clinically significant BOO. For example, monitor these patients for signs and symptoms of urinary retention. Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets should also be administered with caution to patients taking muscarinic antagonist medications for the treatment of OAB.

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets. In some cases, angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema, associated with upper airway swelling, may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets and initiate appropriate therapy and/or measures necessary to ensure a patent airway.

Patients Taking Drugs Metabolized by CYP2D6:

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg Tablets. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone.

## 4.5 Interaction with other medicinal products and other forms of interaction

**•Drugs Metabolized by CYP2D6 (e.g., Metoprolol and Desipramine):**

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme, such as metoprolol and desipramine, is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Mirabegron (Extended-Release) 25 mg &

Solifenacin Succinate 5

mg tablets is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone.

•**Digoxin:**

When given in combination, 100 mg Mirabegron increased mean digoxin Cmax from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng·h/mL (27%). Concomitant administration of 0.25 mg digoxin with a MIRABA-S increased digoxin AUCtau and Cmax by approximately 10% and 14%, respectively When initiating a combination of MIRABA-S and digoxin, prescribe the lowest dose of digoxin; monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect.

•**Warfarin:**

The mean Cmax of S-and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, Mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated.

## 4.6 Fertility, pregnancy, and lactation

Fertility: No fertility data are available. There were no treatment-related effects of mirabegron on fertility in animals.

Pregnancy: There are no studies with the use of Mirabegron (Extended-Release) 25 mg & Solifenacin Succinate 5 mg tablets in pregnant women to inform drug-associated risk for birth defects or miscarriage.

Lactation: There is no information on the presence of Mirabegron and Solifenacin succinate in human milk, the effects on the breastfed child, or the effects on milk production.

## 4.7 Effects on ability to drive and use machines.

Mirabegron has no or negligible influence on the ability to drive and use machines. Solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue, the ability to drive and use machines may be negatively affected.

## 4.8 Undesirable effects

Most commonly reported undesirable effects with MIRABA-S (> 2% and > placebo and > comparator), were dry mouth, urinary tract infection, constipation, and tachycardia.

**Hypertension:** MIRABA-S can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. MIRABA-S is not recommended for use in patients with severe uncontrolled hypertension.
**Urinary retention:** Urinary retention has been reported to occur in patients with bladder outlet obstruction (BOO) and patients with overactive bladder (OAB). MIRABA-S should be administered with caution to patients with clinically significant BOO and OAB. Monitor these patients for signs and symptoms of urinary retention.
**Angioedema:** Angioedema of the face, lips, tongue, and/or larynx has been reported with MIRABA-S. In some cases, angioedema occurred after the first dose or after multiple doses.

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

## 4.9 Overdose

Overdose of Mirabegron shows increases in pulse rate and systolic blood pressure. Treatment for overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended. Overdosage can potentially result in severe anticholinergic effects.
Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended. The patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1hour, but vomiting should not be induced.

# 5. Pharmacological properties

## 5.1 Pharmacodynamic properties

**Mirabegron:** Urological, urinary antispasmodics

**Solifenacin Succinate:** Urological; Drugs for urinary frequency and incontinence ATC code: Mirabegron: G04BD12, Solifenacin succinate: G04BD08

**Pharmacodynamic effects Mechanism of action**
Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) as demonstrated by in vitro laboratory experiments using the cloned human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although Mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicate that beta-1 AR stimulation occurred at a Mirabegron dose of 200 mg.

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.

## 5.2 Pharmacokinetic properties

**Mirabegron:**

Absorption: After oral administration, it is absorbed to reach maximum plasma concentrations (Cmax) at approximately 3.5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean Cmax and AUC increase more than dose proportionally. A 2-fold increase in dose from 50 mg to 100 mg Mirabegron increased Cmax and AUCtau by approximately 2.9-and 2.6-fold, respectively,whereas a 4-fold increase in dose from 50 to 200 mg Mirabegron increased Cmax and AUCtau 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. Co-administration with a high-fat meal reduced Mirabegron Cmax and AUC by 45% and 17%, respectively. A low-fat meal decreased Mirabegron Cmax and AUC by 75% and 51%, respectively.

Distribution: Mirabegron is extensively distributed in the body. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes.

Metabolism: Mirabegron is metabolized 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 human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor.

Excretion: The terminal elimination half-life (t1/2) is approximately 50 hours. Renal clearance (CLR) is approximately 13 L/h, which corresponds to nearly 25% of CLtot. Renal elimination of Mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary elimination 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 solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered

in the urine and 34% in the feces. Approximately 25% of unchanged Mirabegron was recovered in urine and 0% in feces.

**Solifenacin succinate:**

Absorption: After intake of Solifenacin, maximum Solifenacin plasma concentrations (Cmax) are reached after 3 to 8 hours. The Tmax is independent of the dose. The Cmax and area under the curve (AUC) increase in proportion to the dose between 5 to 40mg. Absolute bioavailability is approximately 90%. Food intake does not affect the Cmax and AUC of Solifenacin.
Distribution: The apparent volume of distribution of Solifenacin following intravenous administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α1-acid glycoprotein.
Biotransformation: Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of Solifenacin.
Elimination: After a single administration of 10 mg [14C-labelled]-Solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

## 5.3 Preclinical safety data

Mirabegron: Pre-clinical studies have identified target organs of toxicity that are consistent with clinical observations. Transient increases in liver enzymes and hepatocyte changes (necrosis and decrease in glycogen particles) were seen in rats. An increase in heart rate was observed in rats, rabbits, dogs and monkeys. Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential in vivo.
No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryofoetal development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36fold 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 14fold 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.
Solifenacin succinate: Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryo fetal 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 Applicable

**6.3 Shelf life**
24 Months

**6.4 Special precautions for storage:**
Store below 30℃

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

**7. Marketing authorization holder and manufacturing site addresses**

**Marketing authorization holder:**

| | |
|---|---|
| Company Name: | Tiba healthcare Ltd. |
| Address: | PO BOX- 243-00623, Nairobi. |
| Country: | Kenya. |
| E-mail: | Tibahealthcare1@gmail.com |

**Manufacturing site address:**

| | |
|---|---|
| Company name: | Salud Care (I) Pvt. Ltd. |
| Address: | Plot No. 435, Kishanpur, Jamalpur, Roorkee, Distt.Haridwar,Uttarakhand. |
| Country: | India |
| E-mail: | naitikpandya@saludcare.co.in |

**8. Marketing authorization number**
CTD10046

**9. Date of first registration**
06/04/2023

**10. Date of revision of the text:**
15/09/2023

**11. Dosimetry:**
Not Applicable

**12. Instructions for Preparation of Radiopharmaceuticals:**
Not Applicable