**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal Product

MIRABEGRON EXTENDED-RELEASE TABLETS 50 MG TABLET

## 2. Qualitative and quantitative composition

Each film coated Extended-Release tablet contains:
Mirabegron.....50 mg

For the full list of excipients see section 6.1.

## 3. Pharmaceutical form

Solid oral dosage form

Extended -Release Tablets

## 4. Clinical particulars

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

**Posology**

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

**Special populations**

Renal and hepatic impairment: Mirabegron Tablet has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 $m^2$ or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

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

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

| | | Strong CYP3A inhibitors(3) | |
|---|---|---|---|
| | | Without inhibitor | With inhibitor |
| Renal impairment(1) | Mild | 50 mg | 25 mg |
| | Moderate | 50 mg | 25 mg |
| | Severe | 25 mg | Not recommended |
| Hepatic impairment(2) | Mild | 50 mg | 25 mg |
| | Moderate | 25 mg | Not recommended |

1. Mild: GFR 60 to 89 mL/min/1.73 $m^2$; moderate: GFR 30 to 59 mL/min/1.73 $m^2$; severe: GFR 15 to 29 mL/min/1.73 $m^2$.
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.

**Gender**: No dose adjustment is necessary according to gender.

**Paediatric population**: The safety and efficacy of Mirabegron in children below 18 years of age have not yet been established.

**Method of administration**

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

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients used in manufacturing process.

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

## 4.4 Special warnings and precautions for use

**Renal impairment**: Mirabegron Tablet has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population.

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

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

**Patients with congenital or acquired QT prolongation**: Mirabegron Tablet, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. Caution should be exercised when administering Mirabegron in these patients.

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

**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. 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 Tablet is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to

89 mL/min/1.73 m2) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as Itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food.

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

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

**Effect of mirabegron on CYP2D6 substrates:** In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron.

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

## 4.6 Fertility, pregnancy and lactation

**Woman of childbearing potential**: Mirabegron Tablet is not recommended in women of childbearing potential not using contraception.

**Pregnancy**: There is limited amount of data from the use of Mirabegron Tablet in pregnant women. Studies in animals have shown reproductive toxicity. This medicinal product is not recommended during pregnancy.

**Breast-feeding**: Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. It should not be administered during breast-feeding.

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

The most common adverse reactions reported for patients treated with Mirabegron Tablet 50 mg during the three 12-week phase 3 double blind, placebo-controlled studies are tachycardia and urinary tract infections.

**Infections and infestations**: Urinary tract infection, Vaginal infection, Cystitis

**Psychiatric disorders**:

Insomnia, Confusional state

**Nervous system disorders**:

Headache, Dizziness

**Eye disorders**: Eyelid oedema
**Cardiac disorders**: Tachycardia, Palpitation, Atrial fibrillation

**Vascular disorders**: Hypertensive crisis

**Gastrointestinal disorders**: Nausea, Constipation, Diarrhoea, Dyspepsia, Gastritis, Lip oedema
**Skin and subcutaneous tissue disorders**: Urticaria, Rash, Rash macular, Rash popular, Pruritus, Leukocytoclastic vasculitis, Purpura, Angioedema

**Musculoskeletal and connective tissue disorders**: Joint swelling

**Renal and urinary disorders:** Urinary retention

**Reproductive system and breast disorders:** Vulvovaginal pruritus

**Investigations:** Blood pressure increased, GGT increased, AST increased, ALT increased

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

## 4.9 Overdose

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

# 5. Pharmacological properties

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Urologicals, urinary antispasmodics

**ATC code:** G04BD12

**Pharmacodynamic effects**
**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.

## 5.2 Pharmacokinetic properties

**Absorption**: After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (Cmax) 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 Cmax and AUC increased more than dose proportionally over the dose range. 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.

**Distribution**: Mirabegron is extensively distributed. The volume of distribution at steady state (Vss) is approximately 1670 L. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. In vitro erythrocyte concentrations of 14C-mirabegron were about 2-fold higher than in plasma.

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

**Elimination**: Total body clearance (CLtot) from plasma is approximately 57 L/h. 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 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.

## 5.3 Pre-clinical safety data

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

No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryo fetal development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36-fold higher than observed at the MHRD. The observed embryo fetal toxicity occurred at doses associated with maternal toxicity. The cardiovascular malformations observed in the rabbit were shown to be mediated via activation of the beta 1 adrenoceptor.

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

**6.1 List of excipients**

- Microcrystalline cellulose BP
- Hydroxypropyl Methyl Cellulose K 100 M BP
- Hydroxypropyl Methyl Cellulose K 15 M BP
- Ethyl Cellulose BP
- Povidone-K 90 BP
- Purified Talc BP
- Magnesium Stearate BP
- Isopropyl Alcohol BP
- Dichloromethane BP
- Dr. Coat IH
- 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°C. Protect from light & moisture.

**6.5 Nature and contents of container**

A yellow colored, round shape, biconvex, film coated extended-release tablet. 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>**

Not Applicable

**7. Marketing Authorization Holder:**

TIBA HEALTHCARE LIMITED

**8. Marketing Authorization Number:**

H2024/CTD10180/21622

**9. Date of first Authorization /renewal of the authorization:**

2024 September 15

**10. Date of revision of text:**

2024 September 15