Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

MIRAHAULT ®-50 (Mirabegron (Extended Release) 50 mg Tablets)

2. Qualitative and quantitative composition

Qualitative composition: Each film coated extended-release tablet contains:
Mirabegron .....50 mg

Excipients ..... q.s.

Color: Ferric Oxide Yellow USPNF

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated Extended –Release tablet. Yellow color elongated shaped film coated extended-release tablet one side break line and plain on other side.

4. Clinical particulars

Posology

Recommended Dosage for Adult Patients with OAB:

The recommended starting dosage of Mirabegron ER Tablets is 25 mg orally once daily. If needed, increase to the maximum dosage of Mirabegron ER Tablets 50 mg orally once daily after 4 to 8 weeks. For administration instructions, *see Dosage and Administration*
Recommended Dosage for Pediatric Patients Aged 3 Years and Older with NDO

For pediatric patients 3 years of age and older, select the appropriate product (Mirabegron ER Tablets) based on the patient's weight.

Recommended

Dosage in Adult Patients with Renal or Hepatic Impairment

Dosage in Adults with Renal Impairment

The recommended dosage of Mirabegron ER Tablets (administered orally once daily) in adult patients with renal impairment is described in TABLE 2 [see Use in Specific Populations (8.6)]. For administration instructions, see Dosage and Administration

Recommended Dosage in Adult Patients with Renal Impairment (Administered Orally Once Daily)

Estimated GFR*	Starting Dose	Maximum Volume
11 kg to less than 22 kg	3 mL (24 mg)	6 mL (48 mg)
22 kg to less than 35 kg	4 mL (32 mg)	8 mL (64 mg)
Greater than or equal to 35 kg	Refer to information in next section	

Pediatric Patients weighing 35 kg or more:

The recommended starting dosage of Mirabegron ER Tablets is 25 mg orally once daily. If needed, increase to a maximum dosage of Mirabegron ER Tablets 50 mg orally once daily after 4 to 8 weeks. For administration instructions, Recommended Dosage in Adult Patients with Renal or Hepatic Impairment

Dosage in Adults with Renal Impairment

The recommended dosage of Mirabegron ER Tablets (administered orally once daily) in adult patients with renal impairment is described in TABLE 2.

Estimated GFR*	Starting Dose	Maximum Volume
eGFR 30 to 89 mL/min/1.73 m^2	25 mg	50 mg
eGFR 15 to 29 mL/min/1.73 m^2	25 mg	50 mg
eGFR < 15 mL/min/1.73 m2 or requiring dialysis	Not recommended	

Method of Administration:

Swallow Mirabegron ER Tablets whole with water. Do not chew, divide, or crush. Take with or without food.

4.3 Contraindications

Mirabegron ER Tablets contraindicated in patients with known hypersensitivity reactions to mirabegron or any inactive ingredients of the tablet

4.4 Special warnings and precautions for use

Increases in Blood Pressure Mirabegron ER Tablets can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Mirabegron ER Tablets is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg). In two, randomized, placebo-controlled, healthy volunteer studies, Mirabegron ER Tablets was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately

3.5/1.5 mm Hg greater than placebo. Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Muscarinic Antagonist Medications for OAB In patients taking Mirabegron ER Tablets, 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 ER Tablets patients; however, Mirabegron ER 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. Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with Mirabegron ER 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 ER 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. 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

Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin succinate, tamsulosin, and oral contraceptives). No dose adjustment is recommended when these drugs are co-administered with mirabegron. Drugs Metabolized by CYP2D6:

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 MYRBETRIQ 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 combination of 5 mg solifenacin and 50 mg mirabegron increased digoxin

AUCtau and Cmax by approximately 10% and 14%, respectively. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the 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

Pregnancy: There are no studies with the use of Mirabegron ER Tablets in pregnant women to inform drug- associated risk for birth defects or miscarriage. Mirabegron administration to pregnant animals during organogenesis resulted in reversible skeletal variations (in rats) at 22-fold (via AUC) the maximum recommended human dose (MRHD) of 50 mg/day and decreased fetal body weights (in rabbits) at 14-fold the MRHD. At maternally toxic exposures in rats (96-fold), decreased fetal weight and increased fetal mortality were observed and, in rabbits (36-fold), cardiac findings (fetal cardiomegaly and fetal dilated aortae) were observed. Lactation: There is no information on the presence of mirabegron in human milk, the effects on the breastfed child, or the effects on milk production. Mirabegron-related material was present in rat milk and in the stomach of nursing pups following administrations of a single 10 mg/kg oral dose of

14C-labeled mirabegron to lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Mirabegron ER Tablets and any potential adverse effects on the breastfed child from Mirabegron ER Tablets or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

Mirabegron ER Tablets may cause serious side effects including: • increased blood pressure. Mirabegron ER Tablets may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking Mirabegron ER Tablets

- inability to empty your bladder (urinary retention).

Mirabegron ER Tablets may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medicines to treat overactive bladder. Tell your doctor right away if you are unable to empty your bladder.

- angioedema. Mirabegron ER Tablets may cause an allergic reaction with swelling of the lips,

face, tongue, throat with or without difficulty breathing. Stop using Mirabegron ER Tablets and tell your doctor right away. The most common side effects of Mirabegron ER Tablets include:

- increased blood pressure
- dizziness
- common cold symptoms (nasopharyngitis)
- joint pain
- dry mouth
- headache
- flu symptoms
- constipation
- urinary tract infection
- sinus (sinus irritation)
- back pain
- inflammation of the bladder (cystitis) The most common side effects of Mirabegron ER

Tablets

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested 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 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 overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other urologicals ATC code: G04B D08
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

5.2 pharmacokinetics properties

Absorption: After oral administration of mirabegron in healthy volunteers, mirabegron 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. This relationship is more apparent at doses above 50 mg. In the overall population of males and females, 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. Distribution: Mirabegron is extensively distributed in the body. The volume of distribution at steady state (Vss) is approximately 1670 L following intravenous administration. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. Based on an in vitro study, erythrocyte concentrations of 14C-mirabegron were about 2-fold higher than in plasma. 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. 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 healthy subjects who are genotypically poor metabolizers of CYP2D6, mean Cmax and AUCtau were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol

dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6. Excretion : Total body clearance (CLtot) from plasma is approximately 57 L/h following intravenous administration. 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.

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.

5.3 Preclinical safety data

Carcinogenicity Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher than the MRHD in rats and 21 to 38-fold higher than the MRHD in mice than the human systemic exposure at the 50 mg dose.

Following the administration of 160 mg

Mutagenesis Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22-fold the MRHD in women and 93-fold the MRHD in men.

6. Pharmaceutical particulars

6.1 List of excipients

1. Corn Starch USP 2. Microcrystalline Cellulose Powder USP 3. Hydrocel CW 4000-CR IHS 4. Dibasic Calcium Phosphate Dihydrate USP 5. Povidone(K-30) USP 6. Isopropyl Alcohol $ USP 7. Magnesium Stearate USP 8. Talc USP 9. Drcoat Seal IHS 10. Hypromellose(E-15) USP 11. Titanium Dioxide USP 12. Ferric Oxide Yellow USPNF 13. Methylene Chloride$ USP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months (2Years)

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

3x10Alu-Alu Blister packed in a carton with Product leaflet.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing authorisation holder

Javia International Limited

8. Marketing authorisation number

H2025/CTD11347/24172

9. Date of first authorisation/renewal of the authorisation

2025 July 17

10. Date of revision of the text

2025 July 17