1.3.1.1 PROPOSED PROFESSIONAL INFORMATION FOR MIRABEGRON EXTENDED RELEASE FILM COATED TABLETS

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

URTON 25 25 mg extended release film coated tablets

URTON 50 50 mg extended release film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg or 50 mg mirabegron formulated for oral administration.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

25 mg: Tablet, oval, white to slightly yellowish white, film coated tablet debossed with ‘WM2’ on one side.

50 mg: Tablet, oval, white to slightly yellowish white, film coated tablet debossed with ‘WM5’ on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults (including elderly patients)

The recommended dose of **URTON** is 50 mg once daily with or without food.

Special populations

Patients with Renal impairment

No dose adjustment is necessary for patients with mild and moderate renal impairment (eGFR 30 to 89 mL/min/1,73 m^2 as estimated by MDRD). In patients with severe renal impairment (eGFR 15 to 29 mL/min/1,73 m^2), the recommended dose of **URTON** is 25 mg once daily with or without food. **URTON** has not been studied in patients with End Stage Renal Disease (eGFR <15 mL/min/1,73 m^2 or patients requiring haemodialysis) (see section 4.3).

Patients with Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B) the recommended dose of **URTON** is 25 mg once daily with or without food. **URTON** has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). (see section 4.3)

Paediatric population

The safely and efficacy of **URTON** in children below 18 years of age have not been established. Therefore, use in this age group is not recommended.

Method of administration

URTON is to be taken once daily, with liquids, swallowed whole and is not chewed, divided or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of **URTON**.
- Severe end stage renal impairments (eGFR < 15 mL/min/1,73 m^2).
- Severe hepatic impairment (Child-Pugh Class C).
- Severe uncontrol 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

URTON has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1,73 m^2 or patient requiring haemodialysis) and, therefore, it is not recommended for use in this patient population.

In patients with severe renal impairment (GFR 15-29 mL/min/1,73 m^2), dosage reduction is recommended. **URTON** is not recommended for use in patients with

severe renal impairment (GFR 15-29 mL/min/1,73 m^2) concomitantly receiving strong CYP3A inhibitors.

Hepatic Impairment

URTON 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, **URTON** is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors.

Hypertension

URTON can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with **URTON**, especially in hypertension patients. Data are limited in patient with Stage 2 Hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).

Patients with congenital or Acquired QT Prolongation

URTON at therapeutic doses, has not demonstrated clinically relevant QT prolongation in healthy patients. However, since patients with a known history of prolongation or patients who are taking medicines known to prolong QT interval were not included in these studies the effects of mirabegron in these patients in unknown. Caution should be exercised when administering **URTON** in patients with congenital or acquired QT prolongation.(see section 4.5)

Patients with bladder outlet obstruction and patients taking anti-muscarinic medicines

Urinary retention has been reported in patients with bladder outlet obstruction and patients taking antimuscarinic medicines for the treatment of overactive bladder concurrently taking mirabegron. Caution should be observed when **URTON** is administered to patients with clinically significant BOO and patients taking anti-muscarinic medicines for the treatment of OAB.

4.5 Interaction with other medicines and other forms of interaction

Clinically relevant medicine interactions between mirabegron and medicinal products that inhibit, induce or are a substrate for one of the cytochrome P450 (CYP) isozymes or transporters are not expected, except for the inhibitory effect of mirabegron on the metabolism CYP2D6 substrates. Mirabegron, as in **URTON**, is transported and metabolised through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2 and OCT3. Sulfonylurea hypoglycaemic medicines, glibenclamide (a CYP3A substrate), gliclazide (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP3A4 substrate) may not affect the *in vitro* metabolism of mirabegron. Mirabegron may not affect the metabolism of glibenclamide or tolbutamide. Studies of **URTON** 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. **URTON** is unlikely to inhibit the metabolism of co-administered medicines metabolised by following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1. **URTON** did not induce CYP1A2 or CYP3A. **URTON** inhibited P-gp-mediated medicines

transport at high concentrations. **URTON** may not cause clinically relevant inhibition of OCT-mediated drug transport.

Effect of enzyme inhibitors

Mirabegron exposure was increased 1,8-fold in healthy volunteers, also taking ketoconazole, a strong inhibitor of CYP3A/P-gp. Administration of mirabegron is inadvisable in patients with moderate hepatic impairment (Child-Pugh Class B) simultaneously receiving strong CYP3A inhibitors. **URTON** is not recommended in patients with severe renal impairment or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see section 4.4).

Effect of enzyme inducers

Dose adjustment is not required for **URTON** when administered concomitantly with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

Effect of URTON on CYP2D6 substrates

Caution is advised if **URTON** is co-administered with medicines that are significantly metabolised by CYP2D6 and have a narrow therapeutic index such as haloperidol, risperidone, thioridazine and Type 1C antidysrhythmics (e.g. flecainide, propafenone, clomipramine). Caution should also be taken if URTON is co-administered with CYP2D6 substrates that are individually dose titrated.

Effect of URTON on transporters

The lowest dose of digoxin should be prescribed initially, for patients who are commencing a combination of **URTON** and digoxin. Serum digoxin concentrations should be closely observed and utilized for the titration of digoxin dose to attain the desired clinical effect. The inhibition potential of P-gp by mirabegron should be considered when **URTON** is combined with sensitive P-gp substrates such as dabigatran.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

It is recommended that **URTON** be avoided during pregnancy.

Breastfeeding

Mirabegron may be present in human milk.

URTON should not be administered to mothers who are breastfeeding their infants.

4.7 Effects on ability to drive and use machines

URTON may cause dizziness, somnolence and blurred vision which may have an influence on the ability to drive and use machines. See section 4.8 below.

4.8 Undesirable effects

Infections and Infestations

Frequent:	Urinary tract infection
Less frequent:	Vaginal infection, cystitis

Immune system disorders

Less frequent: angioedema

Psychiatric disorders

Frequency unknown: Insomnia

Nervous system disorders

Less frequent: Dizziness, somnolence, blurred vision

Frequency unknown: Headache

Eye disorders

Less frequent: Eyelid oedema

Cardiac disorder

Frequent: Tachycardia

Less frequent: Palpitations, atrial fibrillation

Vascular disorders

Frequency unknown: Hypertensive crisis

Gastrointestinal disorders

Less frequent: Dyspepsia, gastritis and lip oedema

Frequency unknown: Nausea, constipation, diarrhoea

Skin and subcutaneous tissue disorders

Less frequent: Urticarial rash, macular rash, popular rash, pruritus, ~~angioedema~~ pruritus, leukocytoclastic vasculitis and purpura

Musculoskeletal and connective tissue disorder

Less frequent: Joint swelling

Reproductive system and breast disorder

Less frequent: Vulvovaginal pruritus

Investigations

Less frequent: Increased blood pressure, increase GGT, increase AST, increase ALT

Renal and urinary disorders:

Frequency unknown: Urinary retention

Post-Marketing

Immune system Disorders:

Less frequent: Angioedema

Nervous System disorders:

Frequent: Headache, dizziness

Psychiatric Disorders:

Frequency unknown: Insomnia

Vascular Disorders:

Less frequent: Hypertensive crisis

Gastrointestinal Disorders:

Frequent: Nausea, constipation, diarrhoea

Renal and urinary disorders:

Less frequent: Urinary retention

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

At dose of 300 and 400 mg, adverse events reported included palpitations, increased pulse rate exceeding 100 bpm and increased systolic blood pressure. Treatment for overdose should be symptomatic and supportive. In 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

Mechanism of action

Mirabegron is a selective beta 3-adrenoceptor agonist. Mirabegron has shown relaxation of bladder smooth muscle in rat and human isolated tissue. Data from animal models indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

Pharmacodynamic effects

Urodynamics

URTON at doses of 50 mg and 100 mg once daily shows no effect on cystometry parameters. In patients with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) mirabegron may not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate.

Effect on QT interval

Mirabegron may increase the heart rate on ECG in a dose dependent manner across the 50 mg to 200 mg dose range. The maximum mean difference in heart rate may range from 6,7 bpm with mirabegron 50 mg up to 17,3 bpm with mirabegron 200 mg.

Effect on Pulse Rate and Blood Pressure in Patients with Overactive Bladder (OAB)

No clinically relevant changes may be seen in the blood pressure or pulse rate in OAB patients (means age of 59 years) using 50 mg or 100 mg daily.

Effect of intraocular pressure (IOP)

Mirabegron 100 mg once daily does not increase IOP in healthy patients after 56 days of treatment.

5.2 Pharmacokinetic properties

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentration (C_{max}) between 3 and 4 hours. The absolute bioavailability may increase from 29 % at a dose of 25 mg to 35 % at a dose of 50 mg. Mean C_{max} and AUC may increase more than dose proportionally over the dose range. A 2-fold increase in dose from 50 mg to 100 mg mirabegron may increase 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 increase C_{max} and AUC_{tau} by approximately 8,5- and 6,5-fold. Steady state concentrations may be 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 (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 erythrocytes concentrations of ^{14}C-mirabegron is about 2-fold higher than in plasma.

Metabolism

Mirabegron is metabolised via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulation component following a single dose of ^{14}C-mirabegron. Two major metabolites may be observed in human plasma; both are phase 2 glucuronides representing 16 % and 11 % of total exposure. These metabolites are not pharmacologically active. *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 CYP34 and CYP2D6.

Elimination

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. the terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25 % of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and ranges from approximately 6,0 % after a daily dose of 25 mg to 12,2 % after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron to healthy volunteers, approximately 55 % of the radiolabel may be recovered in the urine and 34 % in the faeces. Unchanged mirabegron accounts for 45 % of the urinary radioactivity,

indicating the presence of metabolites. Unchanged mirabegron may account for the majority of the faecal radioactivity.

Effect of food on absorption

Co-administration of a 50 mg tablet with a high-fat meal may reduce mirabegron C_{max} and AUC by 45 % and 17 %, respectively. A low-fat meal may decrease mirabegron C_{max} and AUC by 75 % and 51 % respectively. Mirabegron can be taken with or without food at the recommended dose.

Characteristics in specific groups

Age

No dose adjustment is necessary for the elderly. The C_{max} and AUC of mirabegron and its metabolites following multiple oral doses in elderly patients (≥ 65 years) may be similar to those in younger patients (18 to 45 years).

Gender

Dose adjustment may be necessary based on gender. The C_{max} and AUC may be approximately 40 % to 50 % higher in females than in males. Genders differences in C_{max} and AUC may be attributed to differences in body weight and bioavailability.

Renal impairment

Following single dose administration 100 mg mirabegron in patients with mild renal impairment (eGFR 60 to 89 mL/min/1,73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC may increase by 6 % and 31 % relative to patients with

normal renal function. In patients with moderate renal impairment (eGFR 30 to 59 mL/min/1,73 m^2), C_{max} and AUC may increase by 23 % and 66 %, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1,73 m^2), mean C_{max} and AUC values may be 92 % and 118 % higher. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1,73 m^2 or patients requiring haemodialysis).

Hepatic Impairment

Following single dose administration of 100 mg mirabegron in patients with mild hepatic impairment (Child-Pugh Class A) mean mirabegron C_{max} and AUC may increase by 9 % and 19 % relative to volunteers with normal hepatic function. Patients with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values may be 175 % and 65 % higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Polyethylene oxide

Polyethylene glycol

Hydroxypropyl cellulose

Butylated Hydroxytoluene

Magnesium stearate

Film coating

Hypromellose 2910, 6 cP

Titanium dioxide

Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months at or below 25 °C.

6.4 Special precautions for storage

Keep the HDPE bottle tightly closed.

Keep blisters in the outer carton until required for use.

6.5 Nature and contents of container

Blisters (consisting of plain aluminum foil and cold forming foil) in cartons containing 30, 90 or 500 tablets.

HDPE bottles with child-resistant closure of polypropylene (PP) and a silica gel desiccant containing 30, 90 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a medicine or waste materials derived from such medicine and other handling of the product

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

7. MARKETING AUTHORISATION HOLDER

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

URTON 25 mg – 54/18.10/0030

URTON 50 mg – 54/18.10/0031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 November 2022

Date of latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable