TABLE OF CONTENTS – CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION OCTOBER 2023

SCHEDULING STATUS: S4 3

1. NAME OF THE MEDICINE 3

2. QUALITATIVE AND QUANTITATIVE COMPOSITION 3

3. PHARMACEUTICAL FORM 3

4. CLINICAL PARTICULARS 3

4.1 Therapeutic indications 3

4.2 Posology and method of administration 4

4.3 Contraindications 6

4.4 Special warnings and precautions for use 7

4.5 Interaction with other medicines and other forms of interaction 10

4.6 Fertility, pregnancy and lactation 12

4.7 Effects on ability to drive and use machines 13

4.8 Undesirable effects 13

4.9 Overdose 15

5. PHARMACOLOGICAL PROPERTIES 15

5.1 Pharmacodynamic properties 15

5.2 Pharmacokinetic properties 17

6. PHARMACEUTICAL PARTICULARS ..... Error! Bookmark not defined.

6.1 List of excipients 18

6.2 Incompatibilities 19

6.3 Shelf life 19

6.4 Special precautions for storage 19

6.5 Nature and contents of container 19

6.6 Special precautions for disposal 19

7. HOLDER OF CERTIFICATE OF REGISTRATION 20

8. REGISTRATION NUMBERS 20

VR

9. DATE OF FIRST AUTHORISATION 20

10. DATE OF REVISION OF THE TEXT 20

VR

CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION OCTOBER 2023

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BAQUIMAK 100 mg (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg Bedaquiline fumarate

Contains sugar: 152,91 mg lactose monohydrate

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

BAQUIMAK 100 mg: White to off white, round biconvex, uncoated tablets, debossed with “J” & “47” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BAQUIMAK 100 mg is indicated, as part of combination therapy, for multi-drug resistant pulmonary tuberculosis in HIV negative or HIV positive adult patients ≥ 18 years of age who are not taking antiretroviral.

VR

Safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** in HIV patients on treatment with antiretroviral (ARV) medicines have not been established.

Safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** beyond 120 weeks have not been established

4.2 Posology and method of administration

Posology

BAQUIMAK 100 mg should only be administered as part of a multi drug resistant tuberculosis (MDR-TB) regimen. It is recommended that **BAQUIMAK 100 mg** is administered by directly observed therapy (DOT). MDR-TB is defined as *in vitro* resistance of the patient's isolate to at least isoniazid and rifampicin.

The recommended dosage of **BAQUIMAK 100 mg** for MDR-TB is:

• Weeks 1 – 2: 400 mg (4 tablets of 100 mg) once daily

• Weeks 3 – 24: 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses)

The total duration of treatment with **BAQUIMAK 100 mg** is 24 weeks. Data on longer treatment duration is very limited. In patients with extensive drug resistance, where **BAQUIMAK 100 mg** is considered necessary beyond 24 weeks to obtain a curative treatment, a longer duration of therapy may be considered only on a case by case basis and under close safety surveillance (see section 4.8).

The prescribing medical practitioner should refer to international (e.g. WHO guidelines) and national/local TB treatment guidelines for direction on selection and duration of use of companion medicines with **BAQUIMAK 100 mg**. **BAQUIMAK 100 mg** should only be used in combination with at least 3 medicines to which the patient's isolate has been shown to be susceptible in vitro. If *in vitro* testing results are unavailable, treatment may be initiated with **BAQUIMAK 100 mg** in combination with at least 4 other medicines to which the patient's isolate is likely to be susceptible.

VR

Throughout treatment with, and following the last intake of **BAQUIMAK 100 mg**, patients should continue to take their companion medicines in accordance with international, national/local TB treatment guidelines and local MDR-TB treatment practice. Refer to the prescribing information of the medicines used in combination with **BAQUIMAK 100 mg** for their specific dosing recommendations.

Missed doses

Patients should be advised of the need to take **BAQUIMAK 100 mg** as prescribed. Compliance with the full course of therapy must be emphasised.

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule.

From week 3 onwards, if a dose is missed, patients should take the missed dose, and adjust the dosing schedule to ensure that the total dose of **BAQUIMAK 100 mg** during the 7 day period does not exceed 600 mg (taken as 3 intakes of 200 mg each, separated by at least 24 hours).

Do not exceed the recommended dosages.

Paediatric population

The safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** in children and adolescents less than 18 years of age have not been established.

Special populations

Elderly populations

There are limited data on the use of bedaquiline as contained in **BAQUIMAK 100 mg** in elderly patients.

Hepatic impairment

The pharmacokinetics of bedaquiline as contained in **BAQUIMAK 100 mg** were assessed after single-dose administration to subjects with moderate hepatic impairment (Child-Pugh B) (see

VR

section 5.2). Based on these results, no dose adjustment is necessary for **BAQUIMAK 100 mg** in patients with mild or moderate hepatic impairment.

BAQUIMAK 100 mg has not been studied in patients with severe hepatic impairment and is not recommended in this population. (see section 4.3).

Renal impairment

Bedaquiline as contained in **BAQUIMAK 100 mg** has been mainly studied in patients with normal renal function. Renal excretion of unchanged bedaquiline as contained in **BAQUIMAK 100 mg** is insignificant (< 0,001 %). No dose adjustment is required in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring haemodialysis or peritoneal dialysis, **BAQUIMAK 100 mg** should be used with caution (see section 5.2).

Method of administration

BAQUIMAK 100 mg should be taken orally with food, as administration with food increases oral bioavailability (see section 5.2). It is recommended that the **BAQUIMAK 100 mg** tablet be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance (i.e. bedaquiline) or any of the excipients listed in section 6.1
- Congenital QT prolongation
- Patients with uncontrolled cardiac dysrhythmias
- Concomitant use with medicines known to prolong the QTc interval to time intervals known to induce serious dysrhythmias
- Patients with severe hepatic impairment (Child Pugh C)

VR

4.4 Special warnings and precautions for use

HIV-TB co-infected patients

There are no clinical data on safety and efficacy on the combined use of antiretroviral medicines and **BAQUIMAK 100 mg** in HIV/MDR-TB co-infected patients and only limited clinical data on the use of **BAQUIMAK 100 mg** in HIV/MDR-TB co-infected patients (n = 22) who were not receiving antiretroviral (ARV) therapy (see section 4.5)

There is limited information on interactions between **BAQUIMAK 100 mg** (bedaquiline) and medicines that may increase or decrease bedaquiline concentrations. The use of systemic potent CYP3A4 inhibitors with **BAQUIMAK 100 mg** should be avoided, as there may be an increased risk of **BAQUIMAK 100 mg** associated toxicity (see section 4.5)

General

The safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** for the treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. The safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** for the treatment of medicine-sensitive TB has not been established. In addition, there are no data on the treatment with bedaquiline as contained in **BAQUIMAK 100 mg** of extra-pulmonary TB (e.g. central nervous system). The safety and efficacy of bedaquiline as contained in **BAQUIMAK 100 mg** for the treatment of infections caused by non-tuberculous mycobacteria (NTM) have not been established.

Therefore, use of **BAQUIMAK 100 mg** in these settings is not recommended.

Cardiovascular safety

During clinical trials with bedaquiline a prolongation of QTc interval was observed (see section 4.8). An ECG should be obtained prior to and after initiation of therapy with BAQUIMAK 100 mg to monitor the QTc interval. Serum potassium, calcium and magnesium should be obtained at baseline and corrected if abnormal. Follow-up

VR

monitoring of electrolytes should be performed if QT prolongation is detected (See sections 4.4 and 4.8).

BAQUIMAK 100 mg treatment initiation is not recommended in patients with:

• Heart failure

• QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat ECG) (see section 4.3), or

• A personal or family history of congenital QT prolongation.

• A history of or ongoing hypothyroidism.

• A history of or ongoing bradydysrthymia.

• A history of Torsade de Pointes.

If necessary, BAQUIMAK 100 mg treatment initiation could be considered in these patients after a favourable benefit risk assessment and with frequent ECG monitoring.

BAQUIMAK 100 mg treatment must be discontinued if the patient develops:

• Clinically significant ventricular dysrhythmias.

• A QTcF interval of > 500 ms (confirmed by repeat ECG).

An additive or synergistic effect on QT prolongation of BAQUIMAK 100 mg when co-administered with other medicines that prolong the QT interval (including delamanid) cannot be excluded (see section 4.5). Caution is recommended when prescribing BAQUIMAK 100 mg concomitantly with medications with a known risk of QT prolongation. In the event that co-administration of such medicinal products with BAQUIMAK 100 mg is necessary, clinical monitoring including frequent ECG assessment is recommended.

Concomitant administration of BAQUIMAK 100 mg with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin and sparfloxacin) should be avoided.

Mean increases from baseline in QTcF were larger in subjects with concomitant clofazimine use than in subjects without concomitant clofazimine use (see section 4.5). In the event that co-administration of clofazimine with BAQUIMAK 100 mg is necessary,

VR

clinical monitoring including frequent ECG assessment is recommended.

Warnings on interactions

CYP3A4 inducers/inhibitors

Bedaquiline as contained in **BAQUIMAK 100 mg** is metabolised by CY3A4 and its exposure may therefore be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4 (see section 4.5).

Co-administration of **BAQUIMAK 100 mg** and medicines that induce CYP3A4 may decrease **BAQUIMAK 100 mg** plasma concentrations and reduce its therapeutic effect. Co-administration of strong CYP3A4 inducers, such as rifamycins (i.e, rifampicin; rifapentine and rifabutin) or moderate CYP3A4 inducers (i.e. efavirenz, St. John's wort, carbamazepine, etc.) used systemically should therefore be avoided during treatment with **BAQUIMAK 100 mg**.

Co-administration of **BAQUIMAK 100 mg** and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to **BAQUIMAK 100 mg**, which could potentially increase the risk of adverse reactions. Therefore, the combination of **BAQUIMAK 100 mg** and moderate or strong CYP3A4 inhibitors (such as ciprofloxacin, erythromycin, fluconazole, clarithromycin, ketoconazole, itraconazole, ritonavir) used systemically for more than 14 consecutive days should be avoided.

Resistance to bedaquiline

Bedaquiline must only be used in an appropriate combination regimen for MDR-TB treatment as recommended by official guidelines, such as from WHO, to reduce the risk of development of resistance to bedaquiline.

Mortality

In the 120-week C208 trial where bedaquiline was administered for 24 weeks in combination with a background regimen, more deaths occurred in the bedaquiline treatment group than in

VR

the placebo group (see section 4.8). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with bedaquiline as contained in **BAQUIMAK 100 mg** treatment.

Hepatic safety

Increases in transaminases or aminotransferase elevations accompanied by total bilirubin ≥ 2x ULN were seen in clinical trials during administration of bedaquiline as contained in **BAQUIMAK 100 mg** with the background regimen (see section 4.8). Patients should be monitored during treatment. If AST or ALT exceeds 5 times the upper limit of normal, then the regimen should be reviewed and **BAQUIMAK 100 mg** and/or any hepatotoxic background medicine should be discontinued.

Other hepatotoxic medicines and alcohol should be avoided while on **BAQUIMAK 100 mg**, especially in patients with diminished hepatic reserve.

Excipients

Lactose intolerance and lactase deficiency:

BAQUIMAK 100 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **BAQUIMAK 100 mg**.

Sodium:

This medicine contains less than 1 mmol sodium per tablet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of **BAQUIMAK 100 mg** and the formation of the N-monodesmethyl metaboloite (M2).

In vitro, bedaquiline does not significantly inhibit the activity of any of the CYP450 enzymes tested (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A) and does not induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activities.

VR

CYP3A4 inducers/inhibitors

Bedaquiline as contained in **BAQUIMAK 100 mg** exposure may be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4.

In an interaction study of bedaquiline and rifampicin in healthy subjects, the exposure (AUC) to bedaquiline as contained in **BAQUIMAK 100 mg** was reduced by 52 % [90 % CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of **BAQUIMAK 100 mg** (bedaquiline) due to a decrease in systemic exposure, co-administration of strong CYP3A4 inducers such as rifamycins (i.e. rifampicin, rifapentine and rifabutin) or moderate CYP3A4 inducers used systemically, such as efavirenz, should be avoided during treatment with **BAQUIMAK 100 mg**. (see section 4.4).

Co-administration of bedaquiline and ketoconazole for 4 days in healthy subjects increased the exposure (AUC) to bedaquiline by 22 % [90 % CI (12; 32)] and should be avoided.

Other antimicrobial medicines

The combination of bedaquiline with isoniazid/pyrazinamide in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with **BAQUIMAK 100 mg**.

In a placebo-controlled clinical study in patients with MDR-TB, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cicloserin was observed.

Antiretroviral medicines

There is limited data on the interaction between **BAQUIMAK 100 mg** and antiretroviral medicines.

Lopinavir/ritonavir

In an interaction study of a single dose of bedaquiline and repeated doses of lopinavir/ritonavir, exposure (AUC) to **BAQUIMAK 100 mg** (bedaquiline) was increased by 22 % [90 % CI (11; 34)].

VR

Clinical data on the combined use of lopinavir/ritonavir and bedaquiline in HIV/MDR-TB co-infected patients are not available (see section 4.4).

Nevirapine

Co-administration of nevirapine with a single dose of bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on the combined use of [these nevirapine and **BAQUIMAK 100 mg** in HIV/MDR-TB co-infected patients are not available (see section 4.4).

QT interval prolonging medicines

There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline as contained in **BAQUIMAK 100 mg** and medicines that prolong the QT interval. In a medicine interaction study of bedaquiline as contained in **BAQUIMAK 100 mg** and ketoconazole, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual medicines. An additive or synergistic effect on QT prolongation of **BAQUIMAK 100 mg** when co-administered with other medicines that prolong the QT interval cannot be excluded (see section 4.4).

QT interval and concomitant clofazimine use

In an open label Phase IIb trial, mean increases in QTcF were larger in the 17 subjects who were using clofazimine at week 24 (mean change from reference of 31,9 ms) than in subjects who were not using clofazimine at week 24 (mean change from reference of 12,3 ms). (See section 4.4).

Paediatric population

Medicine interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and breastfeeding has not been demonstrated.

Breastfeeding

It is not known whether bedaquiine or its metabolites are excreted in human milk. In rats,

VR

concentrations of bedaquiline in milk were 6 – to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period.

Women using **BAQUIMAK** should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machines, although no studies on this effect with bedaquiline as contained in **BAQUIMAK 100 mg** have been performed. Patients should be advised not to drive or operate machinery if they experience dizziness while taking **BAQUIMAK 100 mg**.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions were nausea, arthralgia, headache, vomiting and dizziness.

Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Nervous system disorders	Headache, dizziness		
Cardiacdisorders	ECG QT prolonged		

VR

Gastrointestinal disorders	Nausea, vomiting, diarrhoea		
Hepatobiliary disorders	Increased transaminases*		
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia		

*Terms represented by “increased transaminases” included, AST increased, ALT increased, hepatic enzyme increased and abnormal hepatic function

Deaths

In randomised clinical trials with bedaquiline, a higher rate of deaths was seen in the bedaquiline treatment group compared to the placebo treatment group. The observed imbalance in deaths between the two treatment groups is unexplained. No discernible pattern between death and sputim culture conversion, relapse, sensitivity to other medicines used to treat tuberculosis, human immunodeficiency virus status or severity of disease could be observed. During the trial, there was no evidence of antecedent significant QT prolongation or clinically significant dysrhythmia in any of the patients that died.

In another study, 6,9 % of patients died. The most common cause of death was TB. All but one patient who died of TB had not converted or had relapsed. The causes of death in the remaining patients varied.

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

VR

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

4.9 Overdose

There is no experience with the treatment of acute overdose with **BAQUIMAK 100 mg**. General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) should be taken in case of deliberate or accidental overdose. It is advisable to contact a poison information centre to obtain the latest recommendations for the management of an overdose. Since **BAQUIMAK 100 mg** is highly protein-bound, dialysis is not likely to significantly remove **BAQUIMAK 100 mg** from plasma. Clinical monitoring should be considered.

In a study, subjects receiving a single 800 mg dose of bedaquiline,adverse reactions were consistent with those observed in clinical studies at the recommended dose (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.20.2.3 Tuberculostatics

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK05

Mechanism of action

Bedaquiline is a diarylquinoline which inhibits mycobacterial ATP (adenosine 5' –triphosphate) synthase, an enzyme that is essential for the generation of energy in Mycobacterium tuberculosis. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Pharmacodynamic effects:

VR

Bedaquiline is a diarylquinoline with in vitro activity against medicine-sensitive TB (DS-TB), MDR–TB including pre-extensively medicine resistant (pre-XDR-TB) and XDR-TB. Pre-XDR TB is defined as in vitro resistance of the patient's isolate to: (1) isoniazid, (2) rifampicin and (3) either a fluoroquinolone or at least one of three injectable second-line medicines (amikacin, capreomycin or kanamycin).

XDR-TB is defined as in vitro resistance of the patient's isolate to: (1) isonaizid, (2) rifampicin, (3) a fluoroquinolone and (4) at least one of three injectable second-line medicines (amikacin, capreomycin or kanamycin).

Bedaquiline demonstrates selectivity for mycobacterial (prokaryotic) ATP synthase as opposed to mammalian (eukaryotic) ATP synthase. Bedaquiline has low activity for human ATP synthase in mitochondria (IC50 > 100 µM), resulting in a selectivity index of > 10 000 compared to the mycobacterial ATP synthase (IC50 0,01 µM).

Bedaquiline has activity against M. tuberculosis with a minimum inhibitory concentration (MIC) for medicine-sensitive as well as medicine-resistant strains (MDR including pre-XDR, XDR-strains) in the range of ≤ 0,008 – 0,12 µg/mL. Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23 % to 31 %) in humans and lower antimycobacterial activity (4- to 6-fold lower) compared to the parent compound.

The intracellular bactericidal activity of bedaquiline in primary peritoneal macrophages and in a macrophage-like cell line was greater than its extracellular activity. Bedaquiline is also bactericidal against dormant (non-replicating) tubercle bacilli. In the mouse model for TB infection, bedaquiline has demonstrated bactericidal and sterilising activities.

Acquired resistance mechanisms that affect bedaquiline MICs include mutations in the atpE gene, coding for the ATP synthase target, and in the Rv0678 gene, regulating the expression of the MmpS5-MmpL5 efflux pump. Target-based mutations generated in preclinical studies lead to 8- to 133-fold increases in bedaquiline MIC, resulting in MICs ranging from 0,25 to 4,0 micrograms/mL. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to 2- to 8-fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0,25

VR

to 0,50 micrograms/mL. Isolates with efflux-based mutations are also less susceptible to clofazimine.

Commonly susceptible species

Mycobacterium tuberculosis

5.2 Pharmacokinetic properties

Absorption

After oral administration bedaquiline is well absorbed. Maximum plasma concentrations (Cmax) are typically achieved at about 5 hours post-dose. Cmax and the area under the plasma concentration-time curve (AUC) increased proportionally up to the highest dose studied (700 mg single-dose and once daily 400 mg multiple doses). Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. Therefore, bedaquiline should be taken with food to enhance its oral bioavailability.

Distribution

The plasma protein binding of bedaquiline is > 99,9 % in all species tested, including human. In animals, bedaquiline and its active *N-monodesmethyl* metabolite (M2) are extensively distributed to most tissues; however, brain uptake was very low.

Biotransformation

CYP3A4 was the major CYP isoenzyme involved in vitro in the metabolism of bedaquiline and the formation of the *N-monodesmethyl* metabolite (M2).

Elimination:

Based on preclinical studies, bedaquiline is mainly eliminated in faeces. The urinary excretion of unchanged bedaquiline was < 0,001 % of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant. After reaching C_{max}, bedaquiline concentrations decline tri-exponentially. The mean terminal elimination half-life of bedaquiline and the active *N-*

VR

monodesmethyl metabolite (M2) is about 5,5 months. The long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Special populations:

Patients with hepatic impairment:

No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population (see section 4.2).

Patients with renal impairment:

Renal excretion of unchanged bedaquiline is insignificant (< 0,001 %).

In patients with mild to moderate renal impairment, no dosage adjustment is required.

In patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis, bedaquiline should be used with caution and with increased monitoring for adverse effects, as bedaquiline concentrations may be increased due to alteration of medicine absorption, distribution and metabolism secondary to renal dysfunction. As bedaquiline is highly bound to plasma proteins, it is unlikely that it will be significantly removed from plasma by haemodialysis or peritoneal dialysis.

Elderly patients:

There is limited data on the use of bedaquiline in TB patients aged 65 years and older.

In a population pharmacokinetic analysis of TB patients treated with bedaquiline age was not found to influence the pharmacokinetics of bedaquiline.

HIV co-infection

There are no data on the use of bedaquiline in HIV co-infected patients treated with antiretroviral medicines (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Corn starch

VR

Colloidal silicon dioxide

Lactose monohydrate

Polysorbate 20

Croscarmellose sodium

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in a round white 150 cc HDPE container with absorbent cotton and closed with a white child resistant closure packed in an outer carton. Pack sizes include, 188's tablets.

Tablets are packed in aluminium foil laminated on one side and laminated to Alu PVC on the other side. Pack sizes include 6's tablets.

6.6 Special precautions for disposal

No special requirements.

VR

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

BAQUIMAK 100 mg: To be allocated

9. DATE OF FIRST AUTHORISATION

BAQUIMAK 100 mg: To be allocated

10. DATE OF REVISION OF THE TEXT

To be advised

VR