**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**MAKDEFIL 5 mg FC**

Vardenafil hydrochloride equivalent to Vardenafil 5 mg

**MAKDEFIL 10 mg FC**

Vardenafil hydrochloride equivalent to Vardenafil 10 mg

**MAKDEFIL 20 mg FC**

Vardenafil hydrochloride equivalent to Vardenafil 20 mg

**MAKDEFIL 10 mg ODT**

Vardenafil 10 mg orally disintegrating tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **MAKDEFIL 5 mg FC** tablet contains 5 mg Vardenafil hydrochloride equivalent to Vardenafil

Each **MAKDEFIL 10 mg FC** tablet contains 10 mg Vardenafil hydrochloride equivalent to Vardenafil

Each **MAKDEFIL 20 mg FC** tablet contains 20 mg Vardenafil hydrochloride equivalent to Vardenafil

Sugar free

Each **MAKDEFIL 10 mg ODT** uncoated tablet contains 11.85 mg Vardenafil hydrochloride trihydrate equivalent to Vardenafil 10 mg

Contains sugar (lactose anhydrous 48.20 mg) and sweetener (aspartame 6.0 mg).

Excipients:

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Film-coated tablets

**MAKDEFIL 5 mg FC:**

Orange, round, film-coated tablets debossed with ‘L 51’ on one side and plain surface on the other side.

**MAKDEFIL 10 mg FC:**

Orange, round, film-coated tablets debossed with ‘L 52’ on one side and plain surface on the other side.

**MAKDEFIL 20 mg FC:**

Orange, round, film-coated tablets debossed with ‘L 53’ on one side and plain surface on the other side.

Orally disintegrating tablets

**MAKDEFIL 10 mg ODT:**

White to off white, round, biconvex, uncoated tablets debossed with ‘T41’ on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of erectile dysfunction.

### 4.2 Posology and method of administration

***Posology:***

Recommended adult dose:

The recommended starting dose is 10 mg **MAKDEFIL** taken as needed (approximately one hour) before sexual activity.

However, the medicine may be taken anywhere from 25 minutes to at least up to 4 to 5 hours before sexual activity.

The maximum recommended dose frequency is once per day. **MAKDEFIL** can be taken with or without food.

Sexual stimulation is required for a natural response to treatment.

Dose range:

The recommended daily dose of **MAKDEFIL** is 5 to 20 mg.

Based on efficacy and tolerability, the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg once daily.

**Special populations:**

**Elderly (above 65 years):**

Dosage adjustments are not required in elderly patients.

**Children:**

**MAKDEFIL** is not indicated for use in children.

**Patients with hepatic impairment**

No dose adjustment is needed in patients with mild hepatic impairment (Child-Pugh A). Vardenafil (the active ingredient in **MAKDEFIL**) clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B), supporting a starting dose of 5 mg **MAKDEFIL** film-coated tablets, which may subsequently be increased to 10 mg **MAKDEFIL** film-coated tablets or orally disintegrating tablets.

Patients with moderate hepatic impairment (Child-Pugh B) should not **use MAKDEFIL ODT 10 mg**.

The pharmacokinetics of vardenafil has not been studied in patients with severe hepatic impairment (Child-Pugh C) (see Section 5.2).

**Patients with renal impairment:**

No dose adjustment is needed in patients with mild ($CL_{cr}$ > 50 to 80 mL /min), moderate ($CL_{cr}$ > 30 to 50 mL /min), or severe ($CL_{cr}$ < 30 mL/min) renal impairment.

Vardenafil (the active ingredient in **MAKDEFIL**) clearance is reduced in patients with moderate hepatic impairment (Child- 60 Pugh B), supporting a starting dose of 5 mg **MAKDEFIL** Orally disintegrating tablets, which may subsequently be increased to 10 mg **MAKDEFIL** Orally disintegrating tablets.

Patients with moderate hepatic impairment (Child-Pugh B) should not **use MAKDEFIL 10 mg ODT**.

The pharmacokinetics of vardenafil (the active ingredient in **MAKDEFIL**) has not been studied in patients requiring dialysis.

**Method of administration**

**MAKDEFIL** film-coated tablets are for oral use and can be taken with or without food.

**MAKDEFIL 10 mg ODT** is an orally disintegrating tablet that is placed on the tongue and dissolves in the mouth in the presence of saliva. It should be taken by itself without food or liquid in the mouth. It should be taken immediately upon release from the blister. **MAKDEFIL 10 mg ODT** can be taken with or without food.

**4.3 Contra-indications**

Contra-indicated in patients with a known hypersensitivity to the active substance (vardenafil hydrochloride) or any of the excipients listed in section 6.1

**MAKDEFIL** is contra-indicated in patients who are concomitantly treated with nitrates or nitric oxide donors. Doctors should discuss with patients the contra-indications of **MAKDEFIL**. **MAKDEFIL** is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous phosphodiesterase 5 (PDE5) inhibitor exposure.

- Women, new-borns and children.
- End-stage renal disease requiring dialysis.
- Anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).
- Conditions which may predispose to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).
- Hypotension (resting systolic blood pressure of < 90 mmHg).
- Uncontrolled hypertension (> 170/110 mmHg).
- Recent history of stroke, life-threatening arrhythmia or myocardial infarction (within last 6 months).
- Uncontrolled cardiac failure.
- Unstable angina.
- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.
- Bleeding disorders.
- Active peptic ulceration.
- Severe impairment of liver function.
- Concomitant use of **MAKDEFIL** with the HIV protease inhibitors indinavir and ritonavir (see section 4.5).

Concomitant use of vardenafil with the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) in men older than 75 years (see section 4.5). Moderate hepatic impairment (see Section 4.4).

- People with phenylketonuria.
- Patients with rare hereditary lactose intolerance.

## 4.4 Special warnings and precautions for use

**Prior to initiating any treatment for erectile dysfunction, doctors should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. MAKDEFIL should not be used in men for whom sexual activity is not recommended because of their underlying cardiovascular status.**

Serious cardiovascular events including sudden death, tachycardia, myocardial infarction, ventricular tachy-arrythmia, angina pectoris and cerebrovascular disorders (including transient ischaemic attack and cerebral haemorrhage) have been reported in temporal association with vardenafil. Most of the patients in whom these events have been reported had pre-existing cerebrovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to vardenafil, to sexual activity or to a combination of these other factors.

**Effects on QTc interval**

Reported clinical data of the effect of vardenafil on QT interval in healthy males, indicated that vardenafil produced increases in QTc interval.

Recorded post-marketing data study evaluating the effect of combining vardenafil with another medicine of comparable QT effect showed an additive QT effect when compared with either medicine alone.

These observations should be considered when prescribing **MAKDEFIL** to patients with known history of QT prolongation or patients who are taking medications known to prolong the QT interval. Patients taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications or those with congenital QT prolongation, should avoid using **MAKDEFIL**.

**Effect on vision**

Transient vision loss and cases of non-arteritic ischaemic optic neuropathy have been reported in connection with the intake of medicines containing vardenafil, such as **MAKDEFIL**. The patient should be advised that in the case of sudden vision loss, he should stop taking **MAKDEFIL** and consult immediately a doctor. (see Section 4.8).

**Concomitant use of alpha-blockers**

Consistent with vasodilatory effects of alpha-blockers and **MAKDEFIL**, the concomitant use of **MAKDEFIL** with alpha-blockers may lead to symptomatic hypotension in some patients. Concomitant

treatment should only be initiated if the patient is stable on his alpha-blocker therapy (see Section 4.5). In those patients who are stable on alpha-blocker therapy, **MAKDEFIL** should be initiated at the lowest recommended starting dose of 5 mg **MAKDEFIL** film-coated tablets. **MAKDEFIL** may be administered at any time with tamsulosin. In those patients already taking an optimised dose of **MAKDEFIL**, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor including **MAKDEFIL**.

**General:**

The safety and efficacy of combinations of **MAKDEFIL** with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

**The safety of MAKDEFIL 10 mg ODT has not been studied in patients with moderate hepatic impairment, therefore use of MAKDEFIL ODT 10 in these patients is not recommended (see Section 4.3).**

Concomitant use of the potent cytochrome P450 (CYP) 3A4 inhibitors; e.g. ketoconazole, itraconazole, indinavir and ritonavir can be expected to produce markedly increased plasma levels of vardenafil, the active ingredient in **MAKDEFIL** (see Section 4.5).

A maximum dose of 5 mg **MAKDEFIL** film-coated tablets should not be exceeded when used in combination with erythromycin or clarithromycin.

A maximum dose of 5 mg **MAKDEFIL** film-coated tablets should not be exceeded if used in combination with ketoconazole and itraconazole. **MAKDEFIL** must not be taken with dosages of ketoconazole and itraconazole higher than 200 mg (see Section 4.5).

Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see section 4.5)

**Effect on bleeding**

**MAKDEFIL** has not been administered to patients with bleeding disorders or active peptic ulceration. Therefore **MAKDEFIL** should not be given to these patients (see Section 4.3). In humans, **MAKDEFIL** has no effect on bleeding time alone or with acetylsalicylic acid. In vitro studies with human platelets indicate that **MAKDEFIL** alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With super therapeutic concentrations of vardenafil, the active ingredient

in **MAKDEFIL**, a small concentration dependent enhancement of the antiaggregatory effect of sodium nitroprusside, a nitric oxide donor, was observed. The combination of heparin and **MAKDEFIL** had no effect on bleeding time in rats, but this interaction has not been studied in humans.

Aspartame: MAKDEFIL ODT 10 mg contains aspartame, a source of phenylalanine which may be harmful to people with phenylketonuria (see Section 4.3).
Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose- galactose malabsorption or fructose intolerance should not take **MAKDEFIL 10 mg ODT**.

**4.5 Interaction with other medicines and other forms of interaction**

**Nitrates, nitric oxide donors:**

The blood pressure lowering effect of sublingual nitroglycerin (0,4 mg) taken 1 and 4 hours after vardenafil administration were potentiated by vardenafil in healthy middle aged subjects. Concomitant use of **MAKDEFIL** with nitrates is contra-indicated.

**CYP inhibitors:**

Concomitant use with the HIV protease inhibitors indinavir or ritonavir, which are highly potent inhibitors of CYP3A4, is contraindicated (see Sections 4.3 & 4.4).
Vardenafil as in **MAKDEFIL** is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these enzymes may reduce **MAKDEFIL** clearance. Reported clinical data showed:
Cimetidine (400 mg b.i.d.), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and $C_{max}$ when co-administered with vardenafil (20 mg) to healthy volunteers.
Erythromycin (500 mg t.i.d.), a CYP3A4 inhibitor, caused a 4-fold increase in vardenafil AUC and a 3-fold increase in Cmax when co-administered with vardenafil (5 mg) to healthy volunteers.
Ketoconazole (200 mg), which is a potent CYP3A4 inhibitor, caused a 10-fold increase in vardenafil (the active ingredient in vardenafil) AUC and a 4-fold increase in $C_{max}$ when co-administered with vardenafil (5 mg) to healthy volunteers.

Co-administration of vardenafil **MAKDEFIL** (10 mg) with the HIV protease inhibitor indinavir (800 mg t.i.d.) resulted in a 16-fold increase in vardenafil (the active ingredient in vardenafil) AUC and a 7-fold increase in vardenafil $C_{max}$. At 24 hours after co-administration, the plasma levels of vardenafil were approximately 4 % of the maximum vardenafil plasma level ($C_{max}$).

Ritonavir (600 mg b.i.d) resulted in a 13-fold increase in vardenafil $C_{max}$ and a 49-fold increase in vardenafil $AUC_{0-24}$ when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 25, 7 hours.

Concomitant use of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, indinavir or ritonavir can be expected to produce markedly increased vardenafil plasma levels.

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in $C_{max}$. Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and $C_{max}$. When used in combination with a moderate CYP3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4)

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil $C_{max}$.

**Others:**

Vardenafil (20 mg), when co-administered with glibenclamide (glyburide, 3,5 mg), did not affect the relative bioavailability of glibenclamide (no effect on AUC and $C_{max}$ of glibenclamide). There was no evidence that vardenafil (the active ingredient in **MAKDEFIL**) pharmacokinetics were altered by coadministration of glibenclamide.

No pharmacokinetic and pharmacodynamic (prothrombin time and clotting factor II, VII and X) interaction was shown when Warfarin (25 mg) was co-administered with vardenafil (20 mg). Vardenafil pharmacokinetics was not affected by co-administration of Warfarin.

No relevant pharmacokinetic interaction was shown when vardenafil (20 mg), was co-administered with nifedipine (30 or 60 mg). The combined treatment of vardenafil and nifedipine did not lead to pharmacodynamic interaction (as compared to placebo, vardenafil produced mean additional blood

pressure reductions of 5, 9 mmHg and 5,2 mmHg for supine systolic and diastolic blood pressure, respectively).

**Nitrates, nitric oxide donors:**

The blood pressure lowering effect of sublingual nitroglycerin (0,4 mg) taken 1 and 4 hours after **MAKDEFIL** administration were potentiated by **MAKDEFIL** in healthy middle aged subjects. Concomitant use of **MAKDEFIL** with nitrates is contra-indicated.

**Alpha-blockers:**

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil film-coated tablets.

In two interaction studies with healthy normotensive volunteers after forced titration of the alphablockers tamsulosin or terazosin to high doses over 14 days or fewer, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil.

**Concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, MAKDEFIL should be initiated at the lowest recommended starting dose of 5 mg MAKDEFIL. Patients treated with alpha-blockers should not use MAKDEFIL 10 mg ODT as starting dose.**

**MAKDEFIL may be administered at any time with tamsulosin. With other alpha-blockers a time separation of dosing should be considered when MAKDEFIL is prescribed concomitantly (see Section 4.4).**

Lack of pharmacokinetic interaction was shown when digoxin (0,375 mg) in steady-state was co-administered with vardenafil (20 mg) over 14 days every other day. There was no evidence that vardenafil (the active ingredient in **MAKDEFIL**) pharmacokinetics were altered by co-administration of digoxin.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability (AUC) or the maximum concentration ($C_{max}$) of vardenafil.

Bioavailability of vardenafil (20 mg) was not affected by co-administration of the $H_2$-antagonists ranitidine (150 mg twice a day) and cimetidine (400 mg twice a day). vardenafil (10 mg and 20 mg) did

not influence the bleeding time when taken alone or in combination with low dose acetylsalicylic acid (2 x 81 mg tablets).

**MAKDEFIL** (20 mg) did not potentiate the hypotensive effects of alcohol (0, 5 g/kg body weight). The pharmacokinetics of vardenafil was not altered.

Population pharmacokinetic investigations of phase III data revealed no significant effect of acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP3A4-inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin) on the pharmacokinetics of vardenafil.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see section 4.4)

**4.6 Fertility, pregnancy and lactation**

**MAKDEFIL** is not indicated for use by women. There are no studies of vardenafil in pregnant women. There are no fertility data available.

**4.7 Effects on ability to drive and use machines**

As dizziness and abnormal vision or eye disorder were reported in clinical trials with **MAKDEFIL**, patients should exercise caution when driving, operating hazardous machinery or performing hazardous tasks.

**4.8 Undesirable effects**

*Summary of the reported safety profile*

The most frequent adverse reactions include those related to the nervous system such as headaches and dizziness and those related to vascular system such as vasodilatation.

*Tabulated summary of adverse events*

| **System organ class** | **Frequency** | **Undesirable effect** |
|---|---|---|
| **Infections and infestations** | Less frequent | Conjunctivitis |
| **Immune system disorders** | Less frequent | Allergic oedema and angioedema and allergic reaction |

| | | |
|---|---|---|
| **Psychiatric disorders** | Less frequent | Sleep disorder, anxiety |
| **Nervous system disorders** | Frequent | Headache, dizziness |
| | Less frequent | Paraesthesia and dysesthesia, Somnolence, syncope, amnesia, seizure |
| | Frequency unknown | Cerebral haemorrhage |
| **Eye disorders** | Less frequent | Visual disturbance, ocular hyperaemia, visual colour distortions, eye pain and eye discomfort, photophobia, increase in intraocular pressure |
| | Frequency unknown | Non-arteritic anterior ischemic optic neuropathy (NAION), visual disturbances including vision loss, retinal detachment |
| **Ear and labyrinth disorders** | Less frequent | Tinnitus, vertigo |
| | Frequency unknown | Sudden deafness or loss of hearing |
| **Cardiac disorders** | Less frequent | Palpitation, tachycardia, angina pectoris, myocardial infarction, ventricular tachyarrhythmias |
| | Frequency unknown | Sudden death |
| **Vascular disorders** | Frequent | Vasodilatation<br>Flushing |
| | Less frequent | Hypotension<br>Hypertension |
| **Respiratory, thoracic and** | Frequent | Nasal congestion |
| | Less frequent | Dyspnoea, sinus congestion, epistaxis |

| | | |
|---|---|---|
| **mediastinal disorders** | | |
| **Gastrointestinal disorders** | Frequent | Dyspepsia |
| | Less frequent | Nausea, gastrointestinal and abdominal pain, dry mouth, diarrhoea, gastroesophageal reflux disease, gastritis, vomiting |
| **Hepatobiliary disorders** | Less frequent | Increase in transaminases, increase in gamma-glutamyl-transferase |
| **Skin and subcutaneous tissue disorders** | Less frequent | Erythema, rash, photosensitivity reaction |
| **Musculoskeletal and connective tissue disorders** | Less frequent | Back pain, increase in creatine phosphokinase, increased muscle tone and cramping, myalgia |
| **Renal and urinary disorders** | Frequency unknown | Haematuria |
| **Reproductive system and breast disorders** | Less frequent | Increase in erection, priapism |
| | Frequency unknown | Penile haemorrhage, haematospermia |
| **General disorders and administration site conditions** | Less frequent | Feeling unwell, chest pain |

*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.

### 4.9 Overdose

In reported single dose volunteer studies, vardenafil (the active ingredient in **MAKDEFIL)** was tested in doses up to and including 80 mg per day.

When 40 mg was administered twice daily, cases of severe back pain were observed. In cases of overdose, standard supportive measures should be taken as required. Renal dialysis is not expected to accelerate clearance as vardenafil (the active ingredient in **MAKDEFIL)** is highly bound to plasma proteins and not significantly eliminated in the urine.

## 5. PHARMACOLOGICAL PROPERTIES

Category and Class: A 7.1.5 Vasodilators – peripheral

Pharmacotherapeutic group: Urological, drugs used in erectile dysfunction

ATC code: G04BE09

### 5.1 Pharmacodynamic properties

Vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the most abundant phosphodiesterase (PDE) isoenzyme in the human penile corpus cavernosum. PDE5 is responsible for the degradation of cGMP in the corpus cavernosum. By inhibiting PDE5, the enzyme responsible for cGMP degradation in the corpus cavernosum, vardenafil enhances the effect of endogenous nitric oxide (NO), locally released in corpus cavernosum upon sexual stimulation. The inhibition of PDE5 by vardenafil leads to increased cGMP levels in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has little effect in the absence of sexual stimulation. **MAKDEFIL** thus potentiates the natural response to sexual stimulation.

### 5.2 Pharmacokinetic properties

**Absorption**

**MAKDEFIL** is well absorbed after oral administration. In 90 % of the time, $C_{max}$ is reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. Due to a considerable first-pass effect, the mean absolute oral bioavailability is about 15 %. After oral dosing of **MAKDEFIL**, AUC and $C_{max}$ increase almost dose-proportionally over the dose range 5 to 20 mg.

When **MAKDEFIL** is taken with a high fat meal, the rate of absorption is reduced with an increase in the median $T_{max}$ of 60 minutes and a mean reduction in $C_{max}$ of 20 %. The AUC of vardenafil was not affected. After a normal meal (containing 30 % fat), vardenafil's pharmacokinetic parameters ($C_{max}$, $T_{max}$, and AUC) were not affected.

Based on these results **MAKDEFIL** can be taken with or without food.

**Absorption of the ODT:**

The median time to reach $C_{max}$ in patients receiving **MAKDEFIL** 10 mg orally disintegrating tablets in the fasted state varied between 45 to 90 minutes. After administration of 10 mg **MAKDEFIL** orally disintegrating tablets to patients, mean vardenafil AUC was increased by 21 to 29 % while mean $C_{max}$ was 8 to 19 % lower in comparison to 10 mg **MAKDEFIL** film coated tablets. A high fat meal had no effect on vardenafil AUC and $T_{max}$ while it resulted in a mean reduction in vardenafil Cmax by 35 %. Based on these results **MAKDEFIL** 10 mg orally disintegrating tablets can be taken before or after food. If **MAKDEFIL** orally disintegrating tablets tablet is taken with water, the AUC is reduced by 29 % and median $T_{max}$ is shortened by 60 minutes while $C_{max}$ is not affected. **MAKDEFIL** orally disintegrating tablets should be taken without water.

Bioequivalence studies have shown that **MAKDEFIL** 10 mg orally disintegrating tablets is not bioequivalent to vardenafil 10 mg film-coated tablets; therefore, the orally disintegrating tablets formulation should not be used as an equivalent to vardenafil 10 mg film-coated tablets.

**Distribution**

The mean steady-state volume of distribution (Vss) for vardenafil is 208 L, indicating distribution into the tissues.

Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (about 95 % for parent drug or M1). This protein binding is reversible and independent of total drug concentrations.

Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0,00012 % of the administered dose was present in the semen of patients.

**Biotransformation**

Vardenafil is metabolised predominantly by hepatic enzymes via CYP3A4, with some contribution from CYP3A5 and CYP2C9 isoforms.

Mean elimination half-life (t½) is about 4 to 5 hours.

The major circulating metabolite (M1) results from desethylation at the piperazine moiety of vardenafil, and is subject to further metabolism. The plasma elimination half-life of the metabolite M1 is approximately 4 hours, comparable to the parent drug.

Parts of M1 are in the form of its glucuronide-conjugate (glucuronic acid) in systemic circulation. The plasma concentration of non-glucuronidated M1 is about 26 % that of the parent compound. The metabolite M1 shows a phosphodiesterase selectivity profile similar to that of vardenafil and an in vitro inhibitory potency for PDE5 of approximately 28 %.

**Elimination**

The total body clearance of vardenafil is 56 L/h with a resultant terminal half-life of about 4 to 5 hours.

After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91 to 95 % of administered oral dose) and to a lesser extent in the urine (approximately 2 to 6 % of administered oral dose).

**Special populations**

**Elderly patients (above 65 years):**

On average, geriatric males had a 52 % higher AUC than younger males which is within the variability observed in clinical trials.

Vardenafil AUC and $C_{max}$ in geriatric patients taking **MAKDEFIL** 10 mg ODT were increased by 31 to 39 % and 16 to 21 %, respectively, in comparison to patients aged 45 years and below. Vardenafil was not found to accumulate in the plasma in patients aged 45 years and below or in 65 years or over following once-daily dosing of 10 mg orally disintegrating tablets over ten days.

**Patients with renal insufficiency:**

In patients with mild ($CL_{cr}$ > 50 to 80 mL /min), moderate ($CL_{cr}$ > 30 to 50 mL /min), or severe ($CL_{cr}$ < 30 mL /min) renal impairment, vardenafil pharmacokinetics were similar to that of a normal renal function control group. No statistically significant correlation between creatinine clearance and vardenafil plasma exposure (AUC and $C_{max}$) was observed. Based on these data, no dose adjustment is needed in patients with impaired renal function. The pharmacokinetics of vardenafil has not been studied in patients requiring dialysis.

**Patients with hepatic insufficiency:**

In patients with mild to moderate hepatic impairment (Child-Pugh A and B), vardenafil clearance was reduced in proportion to the degree of hepatic impairment.

In patients with mild hepatic impairment (Child-Pugh A), vardenafil's AUC and $C_{max}$ were increased 1,2-fold, compared to healthy control subjects. No dose adjustment is required in patients with mild hepatic impairment.

In patients with moderate hepatic impairment (Child-Pugh B), vardenafil's AUC was increased 2,6-fold and $C_{max}$ was increased 2,3-fold, compared to healthy control subjects. Therefore, in patients with moderate hepatic impairment, a 5 mg starting dose should be considered, which may subsequently be increased to a maximum of 10 mg.

The pharmacokinetics of vardenafil has not been studied in patients with severe hepatic impairment (Child-Pugh C).

### 5.3 Preclinical safety data

**MAKDEFIL's** preclinical data revealed no genotoxicity, carcinogenicity and toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**MAKDEFIL's** Microcrystalline Cellulose (101), Crospovidone (Type A), Hypromellose 2910, Colloidal Silicon Dioxide, Magnesium Stearate VG-EP, Instacoat Orange A05G10191 which contains HPMC 2910/ Hypromellose, Polyethylene Glycol 400, Titanium Dioxide, Iron Oxide Red, Iron Oxide Yellow

**MAKDEFIL 10 mg ODT**: Aspartame, Colloidal Silicon Dioxide (Aerosil 200), Crospovidone (Polyplasdone XL), Lactose Anhydrous (Supertab 21 AN), Microcrystalline Cellulose (Avicel PH 102), Sodium Chloride, Sodium Stearyl Fumarate (Pruv) and Peppermint Flavour (501500TP0504) containing Maize maltodextrin, Natural flavours, E 1450 Modified corn starch and Pulegone.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

**For MAKDEFIL 10 mg & 20 mg FC**

24 months from the date of manufacture for container and blister pack.

**For MAKDEFIL 10 mg ODT**

48 months from the date of manufacture.

**6.4 Special precautions for storage**

Store at or below 25 °C. Protect from light

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

**6.5 Nature and contents of container**

**MAKDEFIL 5 mg FC**:

HDPE Container Pack: 30 tablets contained in a round white HDPE bottle sealed with a child resistant closure with pulp and heat seal liner.

Blister Pack: Tablets are packed in Clear film PVC/PVdC foil as the forming material and plain aluminium foil as the lidding material.

Pack size include 2's, 4's or 12's tablets.

**MAKDEFIL 10 mg FC**:

HDPE Container Pack: 30 tablets contained in a round white HDPE bottle sealed with a child resistant closure with pulp and heat seal liner.

Blister Pack: Tablets are packed in Clear film PVC/PVdC foil as the forming material and plain aluminium foil as the lidding material.

Pack size include 2's, 4's or 12's tablets.

**MAKDEFIL 20 mg FC**:

HDPE Container Pack: 30 tablets contained in a round white HDPE bottle sealed with a child resistant closure with pulp and heat seal liner.

Blister Pack: Tablets are packed in Clear film PVC/PVdC foil as the forming material and plain aluminium foil as the lidding material.

Pack size include 2's, 4's or 12's tablets.

**MAKDEFIL 10 mg ODT**

**Blister Pack:**

Tablets are packed in cold form laminate, 25 µm OPA/45 µm Aluminum foil/60 µm PVC and Plain 30 µm Aluminum foil/6-8 gsm heat seal laquer (HSL) as the lidding material

**Pack size:** 1's, 2's, 4's and 10's.

Not all packs and pack sizes are necessarily marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

## 8. REGISTRATION NUMBER(S)

**MAKDEFIL 5 MG FC**: 51/7.1.5/9014.011

**MAKDEFIL 10 MG FC**: 51/7.1.5/9015.012

**MAKDEFIL 20 MG FC**: 51/7.1.5/9016.013

**MAKDEFIL 10 MG ODT**: 51/7.1.5/0539.538

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2022

## 10. DATE OF REVISION OF THE TEXT

24 May 2024