SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

REMERON® 15 mg Tablet

REMERON® 30 mg Tablet

COMPOSITION

Each REMERON 15 mg film-coated tablet contains 15 mg of mirtazapine.

Contains sugar: lactose monohydrate 114 mg.

Excipients: colloidal anhydrous silica, hydroxypropyl cellulose, magnesium stearate and maize starch.

Coating layer: hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and iron oxide yellow.

Each REMERON 30 mg film-coated tablet contains 30 mg of mirtazapine.

Contains sugar: lactose monohydrate 227 mg.

Excipients: colloidal anhydrous silica, hydroxypropyl cellulose, magnesium stearate and maize starch.

Coating layer: hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron oxide yellow, iron oxide red.

PHARMACOLOGICAL CLASSIFICATION

A.1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mirtazapine is a tetracyclic antidepressant, belonging to the piperazino-azepine group of compounds. Mirtazapine is an antagonist of central α_2-auto and hetero-adrenoceptors which causes an increase in both noradrenaline and serotonin release.

The effect of released serotonin is exerted specifically via 5-HT_1 type receptors, because 5-HT_2 and 5-HT_3 type receptors are specifically blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2-auto and hetero-adrenoceptors and 5-HT_2 receptors and the R(-) enantiomer by blocking α_2 hetero-adrenoceptors and 5-HT_3 receptors.

In one study there was no efficacy difference indicated between the two enantiomers, despite their different receptor affinities.

The potent histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine has modest antagonism on cholinergic activity. Mirtazapine has modest peripheral α_1-adrenergic antagonist activities and has been associated with acute postural hypotension (see **SIDE EFFECTS**).

Pharmacokinetic properties

After oral administration mirtazapine is rapidly and well-absorbed (bioavailability 50 %), reaching peak plasma levels after about 2 hours.

Binding of mirtazapine to plasma proteins is approximately 85 %. The mean half-life of elimination is 20 to 40 hours; (26 hours in males, 37 hours in females); longer half-lives, up to 65 hours have occasionally been recorded and shorter half-lives have been seen in young men. Steady state is reached in about 5 days with 50 % accumulation, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range.

Mirtazapine is extensively metabolised and eliminated via the urine and faeces within 4 days. Major pathways of biotransformation are demethylation and oxidation followed by conjugation. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.

In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxymetabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.

The presentation of mirtazapine is as a racemate. It is not known whether first pass extraction of mirtazapine is stereo-selective, but it is known that the clearance of the two enantiomers is by different metabolic processes. It is not known whether food affects the bioavailability of the two enantiomers.

Population Subgroups

Liver Disease

Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30 % in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON (mirtazapine) to patients with compromised hepatic function (see **DOSAGE AND DIRECTIONS FOR USE**).

Renal Disease

Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11 to 39 mL/min/1,73 m^2] and severe [GFR < 10 mL/min/1,73 m^2] renal impairment had reductions in mean oral clearance of mirtazapine of about 30 % and 50 %

respectively, compared to normal subjects. Caution is indicated in administering REMERON to patients with compromised renal function (see **DOSAGE AND DIRECTIONS FOR USE**).

Elderly Patients

Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25 to 74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40 % lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10 % lower compared to younger females. Caution is indicated in administering REMERON to elderly patients (see **DOSAGE AND DIRECTIONS FOR USE**).

INDICATIONS

Treatment of episodes of major depression.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Children and adolescents under the age of 18 years (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Concomitant monoamine oxidase inhibitors or within 14 days of discontinuation thereof (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

Use in children and adolescents under 18 years of age

REMERON should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently

observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk, should accompany therapy with antidepressants, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of REMERON film-coated tablets should be given to the patient.

Bone marrow depression

Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with REMERON. In the post-marketing period with REMERON cases of agranulocytosis has also been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned patients with an age above 65. One should therefore be alert for symptoms like fever, sore throat, stomatitis or other signs of infections. If such symptoms occur the treatment should be stopped and blood counts taken.

Jaundice

Treatment should be discontinued if jaundice occurs.

Conditions which need supervision

Careful dosing as well as regular and close monitoring is necessary in patients with:

- **Epilepsy and organic brain symptoms:** REMERON should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.
- **Hepatic impairment:** Following a single 15 mg oral dose of REMERON, the clearance of REMERON was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of REMERON was about 55 % increased.
- **Renal impairment:** Following a single 15 mg oral dose of REMERON, in patients with moderate (10 mL/min ≤ creatinine clearance < 40 mL/min) and severe (creatinine clearance < 10 mL/min) renal impairment, the clearance of REMERON was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of REMERON was about 55 % and 115 % increased respectively. No significant differences were found in patients with mild renal impairment (40 mL/min ≤ creatinine clearance < 80 mL/min) as compared to the control group.

- Cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered.
- Low blood pressure.
- **Diabetes mellitus:** In patients with diabetes, antidepressants such as REMERON may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted, and close monitoring is recommended.

The following should be taken into account:

- Worsening psychotic symptoms can occur when REMERON is administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.
- When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
- Post-marketing experience shows that abrupt termination of treatment after long term administration of REMERON may result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea were the most frequently reported. As advised in **DOSAGE AND DIRECTIONS FOR USE,** it is recommended to discontinue treatment with REMERON gradually.
- Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure.
- **Akathisia/psychomotor restlessness:** The use of REMERON has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and a need to move often, accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

- The effect of REMERON (mirtazapine) on QTc interval was assessed in a randomised, placebo and moxifloxacin controlled clinical trial involving 54 healthy volunteers using exposure response analysis. This trial revealed that both 45 mg (therapeutic) and 75 mg (supratherapeutic) doses of mirtazapine did not affect the QTc interval to a clinically meaningful extent. During the post-marketing use of mirtazapine, cases of QT prolongation, Torsades de Pointes, ventricular tachycardia and sudden death, have been reported. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicines (see **INTERACTIONS** and **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**). Caution should be exercised when REMERON is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.
- **Hyponatraemia:** Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of REMERON. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatraemia.
- **Serotonin syndrome:** Interaction with serotonergic active substances: Serotonin syndrome may occur when REMERON is used concomitantly with other serotonergic active substances (see **INTERACTIONS**). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Elderly patients

Elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with REMERON, undesirable effects have not been reported more often in elderly patients than in other age groups.

MAO-Inhibitors

In patients receiving REMERON in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued REMERON and then are started on an MAOI, there have been reports of serious and sometimes fatal reactions e.g. including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures and mental status changes ranging from agitation to coma. REMERON should not be used in combination with a MAOI, or within 14 days of initiating or discontinuing therapy with a MAOI including linezolid (see **CONTRAINDICATIONS** and **INTERACTIONS**).

Effects on ability to drive and use machines

REMERON may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

Lactose

REMERON contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS

Interaction with other medicaments and other forms of interaction:

Pharmacodynamic interactions

- REMERON may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with REMERON.
- REMERON should not be administered concomitantly with MAO Inhibitors~~,~~ including linezolid, or within 2 weeks of cessation of therapy with these agents~~,~~ (see **CONTRAINDICATIONS**).
- In the opposite way, about 2 weeks should pass before patients treated with REMERON should be treated with MAO inhibitors (see **CONTRAINDICATIONS**).
- Co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, methylene blue, SSRI's, venlafaxine, lithium and St. John's Wort - *Hypericum perforatum* - preparations) may lead to an incidence of serotonin-associated effects (serotonin syndrome: see **WARNINGS AND SPECIAL PRECAUTIONS**). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with REMERON.
- REMERON may potentiate the sedative effects of benzodiazepines and other sedatives (including antipsychotics, antihistamine H_1 antagonists, opioids). Caution should be taken when these medicinal products are prescribed together with REMERON.
- REMERON dosed at 30 mg once daily caused a small, but statistically significant increase in the international normalised ratio (INR) in subjects treated with warfarin. As at a higher dose of REMERON a more pronounced effect cannot be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with REMERON.
- The risk of QT prolongation and/or ventricular dysrhythmias (e.g. Torsades de Pointes) may be increased with concomitant use of medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics) and in case of mirtazapine overdose.
- REMERON may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking REMERON.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, and CYP3A4 inducers, increased REMERON clearance about two-fold, resulting in a decrease in average plasma REMERON concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to REMERON therapy, the REMERON dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the REMERON dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of REMERON by approximately 40 % and 50 %, respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with REMERON, the mean plasma concentration of REMERON may increase more than 50 %. Caution should be excercised and the dose may have to be decreased when co-administering REMERON with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of REMERON with paroxetine, amitriptyline, risperidone or lithium.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been demonstrated. Women on REMERON should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE

The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Initial treatment

Adults

The recommended starting dose for REMERON (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In clinical trials the effective dose range was generally 15 to 45 mg/day.

REMERON has an elimination half-life of approximately 20 to 40 hours; therefore, dose changes should not be made at intervals of less than 1 to 2 weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose. With an insufficient response, the dose can be increased up to the maximum dose of 45 mg per day. If there is no response within a further 2 to 4 weeks, the treatment should be stopped.

Elderly

The recommended dose is the same as that for adults. However, in elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

The clearance of REMERON is reduced in elderly patients. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patients, compared to levels observed in younger adults (see **PHARMACOLOGICAL ACTION, Pharmacokinetic properties**).

Children and adolescents under the age of 18 years

REMERON should not be used in children and adolescents under the age of 18 years (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Renal impairment

The clearance of REMERON may be decreased in patients with moderate to severe renal impairment (creatinine clearance < 40 mL/min). This should be taken into account when

prescribing REMERON to this category of patients (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Hepatic impairment

The clearance of REMERON may be decreased in patients with hepatic impairment. This should be taken into account when prescribing REMERON to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see **PHARMACOLOGICAL ACTION, Pharmacokinetic properties** and **WARNINGS AND SPECIAL PRECAUTIONS**).

REMERON has an elimination half-life of 20 to 40 hours and therefore REMERON is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. REMERON may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with REMERON gradually to avoid withdrawal symptoms (see **WARNINGS AND SPECIAL PRECAUTIONS**).

SIDE EFFECTS

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with REMERON in randomised placebo-controlled trials (see below) were somnolence, sedation, dry mouth, increased weight, increase in appetite, dizziness and fatigue.

All randomised placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of REMERON. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1 501 patients (134 person years) receiving doses of REMERON up to 60 mg, and 850 patients (79 person years) receiving placebo.

Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorised incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with REMERON than with placebo, added with adverse reactions from spontaneous reporting.

The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials.

Table 1. Adverse reactions of REMERON

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**
Metabolism and nutrition disorders	Weight increased[1] Increase in appetite[1]			
Psychiatric disorders		Abnormal dreams Confusion	Nightmares[2] Mania Agitation[2]	Aggression

		Anxiety[2, 5] Insomnia[3, 5]	Hallucinations Psychomotor restlessness (incl. akathisia, hyperkinesia)	
Nervous system disorders	Somnolence[1, 4] Sedation[1, 4] Headache[2]	Lethargy[1] Dizziness Tremor	Paraesthesia[2] Restless legs Syncope	Myoclonus
Vascular disorders		Orthostatic hypotension	Hypotension[2]	
Gastrointestinal disorders	Dry mouth	Nausea[3] Diarrhoea[2] Vomiting[2] Constipation[1]	Oral hypoaesthesia	Pancreatitis
Hepatobiliary disorders				Elevations in serum transaminase activities
Skin and subcutaneous tissue disorders		Exanthema[2]		
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia Back pain[1]		
General disorders and		Oedema peripheral[1]		

administration site conditions		Fatigue		

[1]In clinical trials these events occurred statistically significantly more frequently during treatment with REMERON than with placebo.

[2]In clinical trials these events occurred more frequently during treatment with placebo than with REMERON, however not statistically significantly more frequently.

[3]In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with REMERON.

[4]N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardise antidepressant efficacy.

[5]Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under REMERON treatment, development or aggravation of anxiety and insomnia has been reported.

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with REMERON than with placebo).

The frequency of adverse reactions from spontaneous reporting for which no cases in the randomised placebo-controlled patient trials were observed with REMERON has been classified as ‘not known’.

Post-marketing side effects

The reported post-marketing adverse reactions of which the frequency is not known are:

Blood and the lymphatic system disorders: bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia and thrombocytopenia), eosinophilia

Metabolism and nutrition disorders: hyponatraemia

Psychiatric disorders: suicidal ideation[6], suicidal behaviour[6], somnambulism

Nervous system disorders: convulsions (insults), serotonin syndrome, oral paraesthesia, dysarthria

Gastrointestinal disorders: mouth oedema, increased salivation

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis

General disorders and administration site conditions: generalised oedema, localised oedema.

Renal and urinary disorders: urinary retention

Investigations: increased creatine kinase

Musculoskeletal and connective tissue disorders: rhabdomyolysis[7]

Endocrine disorders: hyperprolactinemia (and related symptoms e.g. galactorrhoea and gynecomastia)

[6]Cases of suicidal ideation and suicidal behaviours, including attempted suicide, have been reported during REMERON therapy or early after treatment discontinuation (see **WARNINGS AND SPECIAL PRECAUTIONS**).

[7]Cases of rhabdomyolysis have been reported in association with serotonin syndrome and multi-drug overdose. In the latter, a causative association with mirtazapine cannot be ascertained.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Present experience concerning overdose with REMERON alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses. In these cases QT-prolongation and Torsade de Pointes have also been reported.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

ECG monitoring should be undertaken.

IDENTIFICATION

REMERON 15 mg Tablets are yellow, coated, oval, biconvex tablets coded TZ over 3 on both sides of a score on one side and MSD on the reverse.
REMERON 30 mg Tablets are red-brown, coated, oval, biconvex tablets coded TZ over 5 on both sides of a score on one side and MSD on the reverse.

PRESENTATION

REMERON 15 mg Tablets are packed in child-resistant push-through strips (10 tablets per strip) made of white opaque polyvinyl chloride film and coloured hard aluminium foil, incorporating a heat-seal coating on the side in contact with the tablets. The tablets are packed in folding cartons. Three strips are packed in a carton, together with the approved package insert.
REMERON 30 mg Tablets are packed in child-resistant push-through strips (10 tablets per strip) made of white opaque polyvinyl chloride film and coloured hard aluminium foil, incorporating a heat-seal coating on the side in contact with the tablets. The tablets are packed in folding cartons. Three strips are packed in a carton, together with the approved package insert.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Store in the original pack in order to protect from light and moisture. Keep out of reach of children.

REGISTRATION NUMBERS

REMERON 15 mg: 32/1.2/0481

REMERON 30 mg: 32/1.2/0482

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

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South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date on the registration certificate:

- REMERON 15 mg: 30 July 1998
- REMERON 30 mg: 30 July 1998

Date of the most recent revision: 30 October 2020

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