PROPOSED AMENDED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form):

BERON 15 (Film-coated tablets)

BERON 30 (Film-coated tablets)

COMPOSITION:

BERON 15:

Each film-coated tablet contains 15 mg of mirtazapine.

Contains sugar (lactose).

BERON 30:

Each film-coated tablet contains 30 mg of mirtazapine.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION:

A.1.2. Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Mirtazapine is a tetracyclic antidepressant, belonging to the piperazino-azepine group of compounds. Mirtazapine is centrally acting as a pre-synaptic α2 -antagonist, which increasesthe central noradrenergic and serotonergic neurotransmission. It limits the effectiveness of inhibitory α2 - adrenergic heteroreceptors on serotonergic neurons as well as inhibitory α2 - autoreceptors and 5-HT_{2A} heteroreceptors on noradrenergic neurons, which enhances the release of both amines.
It has antagonistic effects at several post-synaptic serotonin receptor types (including 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors) and can produce gradual downregulation of 5-HT_{2A} receptors. These several actions probably contribute to the antidepressant effect. Mirtazapine also is a histamine H1-receptor antagonist, and, correspondingly, relativelysedating.

Pharmacokinetics:

Mirtazapine is well absorbed (bioavailability ≈ 50%) from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 85 %. Mirtazapine is extensively metabolized in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The N-desmethyl metabolite is pharmacologically active. The mean plasma elimination half-life is 20 – 40 hours. Elimination is via urine (75 %) and faeces (15 %). Mirtazapine displays linear pharmacokinetics within therecommended dose range.

INDICATIONS:

Treatment of major depressive illness.

CONTRA-INDICATIONS:

Hypersensitivity to **BERON**.

Pregnancy and lactation, as there is insufficient clinical data available.

Children, as insufficient clinical data are available.

WARNINGS AND SPECIAL PRECAUTIONS:

Warnings

BERON should be used with caution in patients with epilepsy, hepatic or renal insufficiency, and cardiac disorders such as conduction disturbances, angina pectoris, and recent myocardial infarction, as well as in patients with hypotension.

Careful dosage as well as regular and careful monitoring is necessary in these patients. Caution should also be exercised in patients with diabetes mellitus, psychoses and those witha history of bipolar disorder. Treatment should be stopped if jaundice develops.

Patients should be advised to report any of the following symptoms during treatment: Fever, sore throat, stomatitis, or other signs of infection. These may be signs of bone marrow depression (neutropenia, agranulocytosis). Treatment should be stopped and a blood count performed.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with **BERON** should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non- psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania.

Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **BERON**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, **BERON** should be tapered (SeePRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE.)

Special precautions:

- **Renal and urinary disorders: BERON** has weak antimuscarinic activity, therefore caution should be exercised in patients with micturition disturbances, and
- **(Eye disorders)** closed-angle glaucoma, and raised intra-ocular pressure.
- **Psychiatric disorders:** Patients should be closely monitored during early therapy until improvement in depression is observed because suicide is an inherent risk in depressed patients.

- **BERON** may decrease alertness, judgement, thinking and concentration. Therefore operating machinery or driving a vehicle should be avoided during treatment.

INTERACTIONS:

MAOI: **BERON** should not be used concomitantly or within two weeks of discontinuing a MAOI. *Alcohol:* **BERON** may potentiate the central nervous depressant action of alcohol and patients should therefore be advised to avoid alcohol.

Anxiolytics or Hypnotics: Use of **BERON** may potentiate the sedative effects of anxiolytics and hypnotics. Caution should be taken when these drugs are prescribed together with **BERON**.

PREGNANCY AND LACTATION:

BERON is contra-indicated in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

Tablets should be taken orally.

BERON should be given in an initial daily dose of 15 mg, which may be increased gradually according to clinical response. The usual effective dose lies within the range of 15 to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in 2 equally divided doses.

Changes in dose should be made at intervals of at least 1 to 2 weeks because of the long half-life.

For treatment of acute, depressive episodes, treatment should be continued for at least 6 months.

BERON should be withdrawn gradually to reduce the risk of withdrawal symptoms.

The clearance of mirtazapine may be decreased in elderly patients and in patients with renal or hepatic impairment. This should be taken into account when prescribing **BERON** to this category of patients.

SIDE EFFECTS:

Body as a whole

Common (>1/100 ≤ 1/10): Asthenia, flu like syndrome, increased sweating.

Nervous system disorders

Common (>1/100 ≤ 1/10): Drowsiness or sedation, vertigo.

Uncommon (>1/1 000 ≤ 1/100): Dizziness, headache.

Rare (> 1/10 000 ≤ 1/1 000): Paraesthesia, epileptic seizures, nightmares, agitation, mania, hallucinations, convulsions, tremor, myoclonus and restless legs syndrome.

Metabolism and nutritional disorders

Common (>1/100 ≤ 1/10): An increase in appetite and weight gain.Dry mouth, constipation, nausea.

The following side effects have been reported but the frequencies are unknown: Vomiting,thirst, bitter taste (in the mouth).

Vascular disorders

Common (>1/100 ≤ 1/10): Oedema, peripheral oedema.

Rare (> 1/10 000 ≤ 1/1 000)): Postural hypotension.

Skin and subcutaneous tissue disorders *Common (>1/100 ≤ 1/10):* Oedema.

Rare (> 1/10 000 ≤ 1/1 000): Exanthema.

Hepatobiliary disorders

Uncommon (>1/1 000 ≤ 1/100): Increases in liver enzyme levels have been reported.*The following side effect has been reported but the frequency is unknown:* jaundice.

Blood and lymphatic system disorders

Rare (> 1/10 000 ≤ 1/1 000): Reversible agranulocytosis, leucopaenia andgranulocytopaenia, orthostatic hypotension.

Musculoskeletal and connective tissue disorders

Rare (> 1/10 000 ≤ 1/1 000): Arthralgia and myalgia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no specific antidote for **BERON**. Treatment is symptomatic and supportive.

IDENTIFICATION:

BERON 15

A yellow, biconvex, capsule shaped, film-coated tablet, debossed with “A” on one side and with a score line in between “0” and “8” on the other side.

BERON 30

A reddish brown, biconvex, capsule shaped, film-coated tablet, debossed with “A” on oneside and with a score line in between “0” and “9” on the other side.

PRESENTATION:

BERON 15

30’s: Printed unit cartons containing 3 blister packs (composed of white PVC and silver coloured aluminium foil backing) of 10 tablets each.

BERON 30

30’s: Printed unit cartons containing 3 blister packs (composed of white PVC and silver coloured aluminium foil backing) of 10 tablets each.

STORAGE INSTRUCTIONS:

Store in a cool (at or below 25 °C), dry place. Protect from light and moisture. Do not remove the blister packs from the unit carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

BERON 15: A40 / 1.2 / 0366

BERON 30: A40 / 1.2 / 0367

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

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