Professional information

BASED ON SCIENTIFIC EVIDENCE

SCHEDULING STATUS: S0

KEENMIND®

HARD CAPSULES

- Complementary medicine Category D33.6 (western herbal)
- This unregistered medicine has not been evaluated by SAHPRA for its quality, safety or intended use.

1. NAME OF MEDICINE

KEENMIND® Hard Capsule (160 mg Bacopa monnieri dry extract CDRI 08)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KEENMIND® CAPSULE: each capsule contains:
Bacopa monnieri (L.) Wettst (Bacopa) 160 mg
[Aerial part of the plant, as 160 mg of a 15-12:1 extract standardised to min 5% bacopasides]

Sugar free.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications:

- Improves cognitive function in adults/ Supports cognitive function in healthy adults/ Maintains healthy cognitive function/ Supports mental clarity and supports cognitive function.
- Improves and maintains memory in healthy individuals/ Improves working memory/ Assists in learning retention.
- Assists with concentration/ focus/ keeping to tasks / attention span.
- Traditionally used in Ayurveda for memory and concentration/ Brahmi has a traditional use in Ayurvedic medicine to heighten learning capacity.
- Traditionally used in Ayurvedic medicine as a nerve tonic and to support cardiovascular health.
- Bacopa monnieri has antioxidant properties.
- In vitro and animal studies suggest that Bacopa monnieri has neuroprotective action.
- Beneficial during times of stress/mild anxiety.

4.2. Posology and method of administration

Posology
Adults:
The recommended daily dosage is 2 capsules to be taken with a meal, preferably breakfast.
Special populations
Paediatric population
The recommended daily dosage for children over 7 years is 1 capsule to be taken with a meal, preferably breakfast, or as advised by a healthcare professional.
Elderly
There are no special dosage recommendations for the elderly.
Clinical studies demonstrate effects may be felt within hours however best results have been shown after 3 months of daily use

Method of administration
Oral use.
Capsules should be swallowed whole with some water.

• Contraindications
KEENMIND® is not recommended for use in children under 7 years.
KEENMIND® should not be taken in case of allergy to:
Any other extract of *Bacopa monnieri*
Any other member of the Scrophulariaceae (figwort) family or other composites
Any of the excipients listed in section 6.1
Special warnings and precautions for use
Do not exceed the stated dose.

• Interaction with other medicines and other forms of interactions
No interaction studies have been performed. There are no human clinical studies reporting interactions with drugs, other medicinal products or supplements. Theoretical drug interactions which are based on preclinical evidence of activity for cholinergic drugs, serotonergic drugs, phenobarbital, morphine, chlorpromazine barbiturates and thyroxine, this has not yet been confirmed during clinical studies and it does not reflect on a dose change.

• Fertility, pregnancy and lactation
There is limited data about the use of Bacopa monnieri in pregnant or breast-feeding women.
As a precautionary measure, it is preferable to avoid the use of KEENMIND® during pregnancy and breast-feeding.

• Effects on ability to drive and use machines
No effects on ability to drive and use machines have been reported.

• Undesirable effects
KEENMIND® has shown to be well tolerated. Adverse effects reported during the administration in clinical studies and during post-market surveillance have generally been infrequent, mild and transient.
Gastrointestinal disorders:
Nausea, abdominal pain and diarrhoea .
Frequency is not known.
If other adverse reactions not mentioned above occur, a healthcare professional should be consulted.

Overdose
Clinical effects from overdose in animals and humans so far have not been reported with Bacopa monnieri.

5. PHARMACOLOGICAL PROPERTIES

• Pharmacodynamic properties
Mechanism of action
The mechanisms of action of CDRI 08 and other Bacopa extracts remain mostly conjectural due to the complexity of the chemical composition of the herbal substance and the limited animal studies available up to date.
Bacopa contains several active constituents however pharmacological activity of the ethanolic extract was traced to the mixture of the triterpenoid saponins designated as Bacosides A and B. Other inert components might influence bioavailability of the active components.

Pharmacodynamic effects
Neuropharmacological actions of *Bacopa monnieri* includes: nootropic (cognitive and memory enhancing effects), adaptogenic, and antioxidant effects. Preclinical evidence related to the neuropharmacological actions of *Bacopa monnieri* include:

1) Improves neuronal transmission:
- Promotes neuron connections in areas of the brain linked to memory such as the hippocampus and the basolateral amygdala. Enhances synaptic plasticity and the protein kinase activity in hippocampus.
- Regulation of neurotransmitter serotonin: CDRI 08 increases serotonin in the hippocampus and the serotonin transporter (SERT) level, involved in learning and memory processes.
- Inhibitory effect on acetylcholinesterase (AChE) activity and enhanced Ach level in hippocampus.
- Can cause an increase in cerebellar cGMP.
- Induction of membrane dephosphorylation and increase of protein and RNA turnover in specific regions of the brain.
- Neuroprotection: increases oxidative free radical scavenging activity in the hippocampus, frontal cortex, and striatum. Protects against both aluminium and mercury induced neurotoxicity, while inhibiting interneuronal lipofuscin accumulation and necrotic alteration in the hippocampus and prevents beta-amyloid pigmentation build-up. Expression and regulation of NR1 (sub-unit of N-methyl-D-aspartate receptors which govern learning and memory) and FMRP (fragile X mental retardation protein) associated with synaptic plasticity.
- Increases cerebral blood flow (CBF): increased CBF and vasodilation appears mediated via release of nitric oxide from the endothelium.

2) Adaptogenic:
- Normalises the stress induced alterations in plasma corticosterone and levels of noradrenaline, serotonin and dopamine in the brain and reduces HSP-70 expression most significantly in the hippocampus.
- Normalises changes induced by stress, e.g., prevented the formation of ulcer, reversed adrenal and thymus hypertrophy, spleen hypotrophy, normalized blood sugar etc.

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Behavioural studies in animals have shown that CDRI 08 and other Bacopa extracts improve early phases of memory consolidation, retention and delay extinction significantly in a wide variety of responses as well as having anxiolytic, antidepressant and neuroleptic properties. The ability to reverse amnesic effects of neurotoxins, scopolamine, diazepam and experimental dementia have also been demonstrated. Additionally, it showed a broad spectrum of anticonvulsant profile against chemical, electrical and hypoxic convulsions.

Clinical efficacy and safety

To date, clinical studies of the effects of *Bacopa monnieri* extract CDRI 08 have included studies on acute (the effects on cognitive function are assessed within 1-2 hours of dosing) and chronic effects (over 90 days) of memory enhancement and cognitive function in healthy adults, in adults with age-associated memory impairment and in children with ADHD.
Several double-blinded, randomised, controlled trials provide evidence to suggest that *Bacopa monnieri* extract CDRI 08 is efficacious in improving the retention of new information, improving learning and free recall of information.

Adults and elderly

Four randomised controlled trials of KeenMind in humans have shown improvement in cognitive functions following KeenMind administration.
Stough et al. conducted the first randomised, double-blind, placebo-controlled study of the cognitive enhancing effects of KeenMind (at the dosage of 300 mg) in 46 healthy adults between 18-60 years of age. They found significant improvement in the speed of visual processing, learning rate and memory consolidation measured by the Auditory Verbal Learning Test (AVLT; $p<0.05$) and an improved state of anxiety ($p<0.001$) in the participants who received CDRI 08 compared with those who received placebo, with maximal effects after 12 weeks.

The results from the study by Stough (2001) were replicated by Roodenrys and colleagues (2002) who found that treatment with 300-450 mg KeenMind for 3 months resulted in significantly improved retention of new information: the recall of information (unrelated word pairs) after a short delay.

In a separate study of the nootropic effects of KeenMind in a larger group of participants (107 healthy volunteers, aged between 18 and 60 years) and using a tailored Cognitive Drug Research (CDR) cognitive assessment battery, Stough and colleagues showed that participants receiving the treatment had a significant improvement in working memory and a reduction in false positives in the rapid visual information processing task, compared with participants receiving placebo.

The positive effects on cognitive function with the sustained use of CDRI 08 were also observed in the smaller study of subjects (35 subjects completed the study) with complaints of memory impairment (Raghav et al. 2006). In these subjects, treatment with CDRI 08 produced significant improvement in mental control, logical memory and paired associated learning [8]. Additional studies on the acute effects of CDRI 08 show that cognitive performance can be improved on specific tasks.

Downey and colleagues provide data to support an acute effect of CDRI 08 for this indication with improved performance on the serial 3s subtraction test with a 320mg dose at the first, second and fourth repetition post-dose. This improvement in performance is thought to be due to improvements in information processing and decision making time and is also thought to involve aspects of attention and freedom from distractibility.

CDRI 08 has shown to be well tolerated during clinical studies both during chronic and acute administration. No treatment related serious adverse events including deaths occurred during studies with KeenMind. Reported adverse events were infrequent, mild and transient generally related to gastrointestinal disorders.

Paediatric population

Bacopa monnieri has been traditionally given to children to improve intellectual functions. A clinical trial using *Bacopa monnieri* CDRI 08 has been reported and published.

Following improvements have been shown:

- sentence repetition, logical memory, and pair-associative learning in children with Attention Deficit Hyperactivity Disorder (ADHD).

A review that analysed studies of Bacopa monnieri extract in children and adolescents, including CDRI 08 extract contained in KeenMind, demonstrated improvements in this population after treatment in a number of the memory sub-domain assessments particularly in memory-span. Safety and tolerability data was well reported for the majority of included studies and it was reported that only 2.3% of all participants reporting mild side-effects mostly related to gastrointestinal upset as seen in other patient populations.

• Pharmacokinetic properties

There are as yet no published human pharmacokinetic data on CDRI-08. The peak of the dose-absorption curve in not known, but onset of detectable activity on cognitive functions was demonstrated from one hour post consumption and onset of detectable activity on cognitive functions is at more than 5 weeks, with effects apparent at 12 weeks. Nevertheless, in vivo pharmacokinetic studies have provided information about the bacosides in *Bacopa monnieri* extracts:

• Bacoside A is unlikely to be absorbed through the intestine or to penetrate the blood-brain barrier (BBB), using in silico models. Therefore, the bacosides are likely to undergo transformation in vivo to remove the sugar units as well as other biotransformations, that result in metabolites that may mediate the memory enhancing and cognitive activities.

• After oral administration, the plasma concentration of bacopaside I (BP-I) in rats increased rapidly of three dosages (3, 6, and 12mg/kg) and reached Cmax (ng/mL) of 74.70±14.58, 117.94±16.88 and 197±14.13, respectively within 22 min, then the concentrations declined with the T½ of 50.47–80.37 min. The calculated oral bioavailabilities of BP-I in rats were 7.22%, 9.69% and 8.30% at low (3 mg/kg), middle (6 mg/kg) and high (12 mg/kg) dosage levels, respectively.

• After intravenous injection of 5mg/kg BP-I into mice, the plasma and brain pharmacokinetics of BP-I were determined as the following: Cmax (ng/mL) 10763.78±3148.88SEM plasma and 1506.94±316.47SEM brain and T½ (h) 3.85± 1.38 plasma and 3.54± 0.65 brain respectively, which provided evidence of the ability of BP-I to cross the BBB.

As *Bacopa monnieri* may inhibit acetylcholinesterase and might increase acetylcholine levels, there is a theoretical possibility that it may enhance the effect of acetylcholinesterase inhibitors and increase the risk of cholinergic side effects. Therefore, concurrent use of anticholinergic agents might theoretically decrease the effectiveness of *Bacopa monnieri* or the anticholinergic agents. In addition, as *Bacopa monnieri* exhibits calcium antagonist activity in isolated guinea pig ileum it may theoretically have an impact on calcium channel blocking agents. However, the impact of *Bacopa monnieri* on these agents in humans has not been assessed.

Animal models provide evidence that *Bacopa monnieri* may decrease the toxicity of the drugs morphine and phenytoin and may also potentiate the sedative effects of phenobarbital and chlorpromazine (USP safety review of Bacopa). The clinical implications of these effects has not been assessed.
The use of *Bacopa monnieri* in rats was reported to increase thyroxine concentrations by 41% when administered at 200 mg/kg. Therefore, *Bacopa monnieri* may have a thyroid stimulating role. The clinical implications of this finding have not been assessed.

• Preclinical safety data

CDRI 08 has a high safety margin, as it possesses an LD50 of more than 3000 mg/kg p.o. in both mice and Wistar rats.
Results obtained from various repeated-dose toxicity studies showed CDRI 08 to be safe in Sprague-Dawley rats, Charles Foster rats, Beagle dogs and rhesus monkey.
The genotoxic profile of CDRI 08 was studied in a series of short term in-vitro and in vivo toxicological tests. These studies suggests that CDRI 08 is non-genotoxic and therefore safe for human consumption at non-cytotoxic doses. Another study also demonstrated that CDRI 08 was not genotoxic in bone marrow cells under in vivo experimental condition.

Oral administration of CDRI 08 (pregnant Charles Foster rats and New Zealand white rabbits) during major organogenesis has not revealed any teratogenic effects that linked to the nature or dose of CDRI 08.

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To date there has been no carcinogenic nor reproductive and developmental toxicity studies done for CDRI 08. There is a report suggesting that a *Bacopa monnieri* extract may cause reversible suppression of spermatogenesis and fertility without producing aberrant toxic effects. On the contrary, a recent study results suggest that treatment with CDRI 08 improves sperm quality and spermatogenic cell density and steroidogenic indices in the testis of Parkes mice.

Altogether, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

• List of excipients
Calcium hydrogen phosphate, anhydrous; cellulose, microcrystalline; talc; magnesium stearate; silica colloidal, anhydrous; hydroxypropyl methyl cellulose (HPMC) (E464); titanium dioxide (E171); chlorophyllin-copper complex (E141).

• Incompatibilities
Not applicable.

• Shelf life
36 months

• Special precautions for storage
Store at or below 25 °C.

• Nature and contents of container
The capsules are packed into blisters consisting of transparent (PVC/ PVDC film) on one side and an aluminium foil on the other side. Pack sizes of 30 and 60 hard gelatine capsules. Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

SFI South Africa (Pty) Ltd
121 Mitchell Street
George, 6529
Tel: +27 (44) 874 2927

8. REGISTRATION NUMBER

D540514

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10. DATE OF REVISION OF THE TEXT

July 2022.