PRODUCT PROFILE

N-PEP-12
(MemoProve™)

A Unique Neuroprotective Natural Health Product
to Counteract Age-Associated Memory Impairment

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General Information on N-PEP-12

Description

N-PEP-12 is a unique natural health product ingredient by MemoMind Pharma of Austria. MemoMind Pharma is an affiliate of EVER Neuro Pharma (Austria), a company with long experience in prescription drug development focused primarily on the central nervous system, particularly in the field of peptide therapeutics for dementia. EVER Neuro Pharma was founded in 1934 under the name EBEWE Pharma. EBEWE Pharma previously was owned by BASF and Abbott Laboratories, but became a privately-owned, independent company through a management buy-out. In 2008 EVER Neuro Pharma was established as a spin-off of the former NeuroProducts Division of EBEWE.

EVER Neuro Pharma currently sells prescription drugs in over 50 countries and its state-of-the-art production facilities along with the international headquarters are located in Unterach, Austria. EVER’s production facility follows GMP guidelines for the pharmaceutical industry and is certified by the Austrian Ministry of Health. Drawing from this experience, MemoMind Pharma has set out to develop new, science-based natural health product that support memory function and counteract Age-Associated Memory Impairment (AAMI).

N-PEP-12 is the first clinically proven-effective memory natural health product. It consists of peptone-based neuropeptides and is produced enzymatically from purified nerve cell proteins. The neuropeptides of N-PEP-12 bolster the function of nerve cells by mimicking the effects of neurotrophic factors in the brain and counteract the neurodegenerative changes that occur in the aging brain by providing neuroprotective support for the neurons in the brain.
Patent Situation

Date of Patent: Dec. 12, 2006
Composition

N-PEP-12 is a natural health product which consists of peptone-based neuropeptides. N-PEP-12 is presented in the form of film-coated tablets or capsules. One tablet contains 90 mg of the proprietary neuropeptide blend. N-PEP-12 does not contain any herbal ingredients, sugar, starch, caffeine, yeast, dairy, preservatives, artificial colours or flavours. The recommended daily dosage is 1 tablet.

### Product Facts

<table>
<thead>
<tr>
<th>Serving 1 Tablet</th>
<th>Amount Per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptones</td>
<td>90 mg †</td>
</tr>
</tbody>
</table>

† Daily value not established

Other ingredients: Lactose, Cellulose, Magnesium Stearate, Silicon Dioxide, Enteric coating (cellulose acetate phthalate, titanium dioxide, talcum, triethylcitrate, paraffin).

Manufacturing

N-PEP-12 is produced enzymatically from purified nerve cell proteins and consists of peptone-based neuropeptides. The manufacturing process of the peptones is in accordance with current Good Manufacturing Practice (GMP) guidelines for the pharmaceutical industry and has been inspected and certified by the Austrian Ministry of Health.

Quality Control

The characterisation and quality control of N-PEP-12 is performed using enhanced analytical test methods for the determination of amino acids, total nitrogen content and HPLC-peptide fingerprinting for comparative analysis of different batches of the product. These state-of-the-art quality control procedures ensure that a highly reproducible quality of the product can be warranted.
Safety Information

Peptones are generally recognized as safe (GRAS) by the FDA. Furthermore, there is no evidence of any toxic effects of N-PEP-12 in clinical trials. Since its introduction, over 12 million dosages of N-PEP-12 have been taken by consumers without any safety concerns.

1 21 C.F.R. Subpart B – LISTING OF SPECIFIC SUBSTANCES AFFIRMED AS “GRAS” Sec. 184.1553
Profile of N-PEP-12

Introduction & Scientific Background

The ever increasing life expectancy in the industrialised world causes the demographic profile of our population to shift dramatically. We see a steep increase of the percentage of people in the age groups beyond 65 years, and remarkably, the fastest growing segment of our population are the centenarians, people of an age above 100 years. Modern medicine continues to successfully fight the battle against major fatal illnesses like heart and infectious diseases as well as cancer and contributes significantly to the prolongation of our lives.

With increasing age, however, our physical and mental capabilities tend to decrease if left unattended. A decline of cognitive performance in association with aging is a widespread phenomenon in elderly humans and individuals developing age related memory complaints are at higher risk of developing the clinical picture of dementia later in their life. This typically begins with complaints of short-term memory lapses and the perception of a reduced capability to acquire new information. This widespread phenomenon is considered to be related to the normal aging process and it has been termed Age-Associated Memory Impairment (AAMI)\(^2\). AAMI represents a benign type of cognitive decline which progresses slowly over time\(^3\) and has also been termed Benign Senescent Forgetfulness\(^4\) to highlight the generally benign nature of the condition. It develops gradually and generally affects people who are older than 40 to 50 years of age. Surveys have found that close to 50% of individuals meet the criteria for AAMI at the age of 50 and that this number increases to over 80% for individuals older than 80 years of age.

Although AAMI is considered to be part of the normal aging process and progresses only slowly over time, its effects on memory performance are truly worrying. Research has shown that our memory function declines between age 30 and 70 in the order of 50%.\(^5\) Furthermore, the observed cognitive decline that comes along with AAMI is associated with detectable


N-PEP-12
A unique neuroprotective natural health product to counteract age associated memory impairment

morphological and structural neurodegenerative changes. These changes include neuronal and synaptic loss as well as neurofibrillary tangle formation, which are also known hallmarks of Alzheimer’s Disease pathology.

It is thus conceivable that, if left unattended, the subtle memory complaints that come along with aging may aggravate over time and eventually convert to the clinical diagnosis of a dementing illness. The use of neuroprotective natural health product such as N-PEP-12, therefore represents a valuable approach to counteract the subtle but insidious cognitive decline associated with the aging process. Clinically proven natural health product can help to support healthy memory function and cognitive performance and minimize the risk of developing Age-Associated Memory Impairment.

N-PEP-12

N-PEP-12 is the first clinically proven effective natural health product that supports memory performance and counteracts Age-Associated Memory Impairment after oral administration. N-PEP-12 is produced enzymatically from purified nerve cell proteins and has a unique mode of action.

The patent-pending peptone-based neuropeptide blend of N-PEP-12 contains specific natural neuropeptides that mimic the effects of neurotrophic factors in the brain. These neurotrophic factors are required by brain nerve cells for survival and normal function, they preserve the neuronal network in the brain and they protect the neurons from cell stress and from toxic lesion that occur during the aging process. Experimental studies have shown that N-PEP-12 neuropeptides act in exactly the same manner as these naturally occurring neurotrophic factors. Studies in neuronal cell cultures have demonstrated that N-PEP-12 is neuroprotective by diminishing the neurotoxic effects of glutamate, oxygen free radicals and too high calcium levels, as well as the detrimental effects of an undersupply of oxygen in the brain. Studies using aged animals have shown that N-PEP-12 counteracts age-related neurodegeneration, synaptic loss and disturbances of memory and learning performance.

N-PEP-12 supports the viability of neurons and it stimulates the formation of synaptic contacts between neurons. It thereby preserves the neuronal network in the brain which is the foundation of all our mental abilities and which is prone to degeneration as we age. Thus, unlike other memory products, N-PEP-12 directly counteracts the underlying changes that cause Age-Associated Memory Impairment and helps to support memory performance. Furthermore, the neuropeptides of N-PEP-12 have complex neurochemical effects that are directly associated with acute improvement of memory function. More specifically, they increase glucose transport across the blood-brain-barrier and stimulate glucose utilization by brain cells. N-PEP-12 neuropeptides increase the activity of choline acetyltransferase, an enzyme that is directly involved in the biosynthesis of neurotransmitter substances in the brain, and lead to a long-lasting enhancement of synaptic transmission in specific regions of the brain that are involved in memory processes.

Double-blind, placebo-controlled studies in humans have shown that N-PEP-12 improves memory performance, attention and vigilance in elderly volunteers.

The scientific data available from both experimental and clinical studies of N-PEP-12 is summarized below.

**Neuroprotective Effects of N-PEP-12**

Experimental studies were performed to explore the neuroprotective activity of N-PEP-12 in neuronal cell cultures. More specifically, primary cultures of cortical neurons were pre-treated with N-PEP-12 and subjected to various types of cellular lesions and stress that would simulate conditions that occur in the aging brain. Lesions were induced with sodium cyanate to simulate cytotoxic hypoxia, L-glutamate to induce excitotoxicity, ionomycin to simulate chronic calcium overload and colchicine to induce cytoskeletal disruption. Cellular viability was determined 24h and 48h after the experimental lesion and the results of N-PEP-12 treatment were compared to control cell cultures. The results strongly indicate a neuroprotective effect of N-PEP-12 with a dose-dependent protection of neurons in all lesion models. Cell viability was significantly increased by N-PEP-12 treatment as compared to

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control cell cultures. Figure 1 summarizes the effects of N-PEP-12 in the different lesions for the 24h experiment. Results at 48h yielded essentially similar results.

**Figure 1: Effects of different dosages of N-PEP-12 on neuronal viability in various lesion models**

Values indicate mean optical density (OD) + standard deviation.

Higher OD values indicate increased cell survival. *p<0.05, **p<0.01, ***p<0.001.

In summary, the study demonstrates that N-PEP-12 is a potent neuroprotective agent that can protect vulnerable neurons against metabolic deficits, ischaemic episodes and neurodegenerative processes which occur in the aging brain.
N-PEP-12 improves memory and learning performance in old aged animals

In this study the effects of oral N-PEP-12 intake on memory and learning performance in comparison to placebo treatment were investigated in aged rats. Approximately 18-month-old rats were treated for three months with once daily oral administration of N-PEP-12. Memory and learning performance of the animals was assessed at 1, 2 and 3 months after the onset of treatment using the so-called Morris water maze paradigm. In this test, the animals are trained to find a hidden escape platform in a swimming pool and their memory function as well as the speed of acquisition of information (learning) is measured. After the last behavioural test the animals were sacrificed and brain samples were collected for subsequent histological analysis of synaptic density in the hippocampal formation. The hippocampal formation plays an essential role in memory function and is specifically vulnerable to morphological changes associated with a decline in cognitive function during normal brain aging.

![Graph showing differences in escape latencies between Day 1 and Day 5](image)

**Figure 2: Effects of N-PEP-12 on long term memory in aged rats**

Values indicate the mean difference in time rats needed to find the hidden platform + the standard deviation. Higher values indicate better test performance. **p<0.01.

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The results of the behavioural tests in the Morris water maze show a statistically significant difference between the N-PEP-12 treated group and the control group. At the beginning of the second test series at month 2, the animals treated with N-PEP-12 find the hidden platform in the Morris water maze much faster than the control group. This is evident from the difference in the escape latency between the first and the second training period and it indicates that N-PEP-12 intake improves long term memory in the test animals (Fig 2).

The improved cognitive performance of the N-PEP-12 treated animals correlates with morphological changes in the hippocampus of the animals. More specifically an increase of synaptic density was observed in N-PEP-12 treated animals (Fig 3). These results are in excellent accordance with the observed cognitive effects, since these brain structures are known to be involved in learning and memory mechanisms. It has been demonstrated that a loss of synaptic connectivity in these structures occurs during aging and is a marker of age associated cognitive decline.

The increase in synaptic density and plasticity may induce long term beneficial effects, and potentially can slow down cognitive performance decline with age or reduce the risk of memory decline in the elderly.
N-PEP-12 Enhances Cognitive Function and Brain Bioelectrical Activity in Humans\textsuperscript{11}

Age Associated Memory Impairment is often accompanied by electroencephalographic (EEG) slowing in elderly subjects which is related to alterations in brain neurotransmission systems and neurotrophic responses\textsuperscript{12}.

This study was performed to investigate the effect of a single oral dose of N-PEP-12 on brain bioelectrical activity and on cognitive performance in healthy elderly non-demented subjects. Six healthy elderly individuals with a mean age of 63 years and with subjective memory complaints were enrolled in this study. Cognitive function and the brain bioelectrical activity of the participants were tested before N-PEP-12 intake and 24 hours after administration of 180 mg of N-PEP-12 using a battery of cognitive evaluation scales as well as electroencephalography examination.

In all three memory tests, improvement of cognitive function was evident after N-PEP-12 intake (Fig 4).

\textbf{Figure 4: Effects of N-PEP-12 on Memory Performance}

Values represent mean error scores + standard deviation.
Lower scores represent improvement; *p<0.05; **p<0.01.


Highly significant improvement was observed in two of the tests, the Total Memory Score with approximately 30% improvement and the Word Recognition Task. In the latter, a highly significant improvement of about 46% relative to the baseline performance was evident after intake of N-PEP-12.

These effects indicate that N-PEP-12 supports and potentiates attention and memory functions in elderly adults. This fact has been confirmed by electroencephalographic measurements of the brain bioelectrical activity in these individuals. The intake of N-PEP-12 increased the brain bioelectrical power ratio by increasing the fast alpha activity and decreasing the slow delta activity leading to an acceleration of overall brain activity (Fig 5). The increase in alpha frequencies is consistent with a potential enhancement in arousal-attention mechanisms and the reduction of relative delta activity is in concordance with the activatory action of N-PEP-12 on brain bioelectrical activity.

These observations indicate that N-PEP-12 acts as a potent activator of brain activity even after only a single oral dose. Importantly, no adverse effects were reported and the administration of N-PEP-12 was completely safe and well tolerated.
N-PEP-12 Self-Assessment Study in Elderly Volunteers\textsuperscript{13}

The activating effects of N-PEP-12 were confirmed in a self-assessment study in 20 elderly volunteers. In this study, 20 healthy elderly volunteers (15 female, 5 male) with subjective memory complaints resembling Age Associated Memory Impairment were taking a once daily dose of 90 mg N-PEP-12 for 28 days. The average age of the study participants was 59 years. A self-assessment questionnaire was used to assess the effects of N-PEP-12 in this study. The participants had to answer 29 questions related to their memory performance, their ability to concentrate, their learning capabilities and their general well-being in a four point scale. This questionnaire was used before the onset of N-PEP-12 intake and at the end of the 4-week test period.

Significant improvement was evident after the one month intake of N-PEP-12. Overall, 18 participants out of 20 (90\%) had improvement in at least one of the domains, 70\% had improved memory function, 45\% reported a better concentration, 30\% noted that their ability to learn has significantly increased, and 60\% reported a generally better well-being.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{n-pep-12-self-assessment-study.png}
\caption{Effect of N-PEP-12 on Self-Assessment Scores}
\end{figure}

Values represent \% of study participants who reported improvement after intake of N-PEP-12 for 28 days.

In total, 35% of the participants improved in three domains, and 75% of the participants reported a significantly better performance in at least two domains. Only 2 participants reported no response to N-PEP-12 intake. N-PEP-12 was well tolerated in this study and no adverse effects whatsoever were reported by the study participants.

The investigator of the study, Dr. Dieter Volc, ProSenex, Vienna: “Despite the short intake period, N-PEP-12 has clearly improved these participants. They were clearly more alert and attentive when they came back after the test period. Many wanted to continue taking N-PEP-12 because they felt it helped them to maintain and improve their mental capabilities. I believe N-PEP-12 is a valuable natural health product to support a healthy mental state and to preserve the cognitive abilities during aging.”

**N-PEP-12 improves memory in AAMI – a randomized, double-blind, placebo-controlled trial**

In this study the effects of N-PEP-12 were investigated in a fully randomized, double-blind, placebo-controlled, parallel-group trial comparing a single 90 mg daily dose of N-PEP-12 with placebo. 54 male or female volunteers with 50 years of age or older suffering from mild memory loss were enrolled in this study. The intake period was thirty days and cognitive evaluations were performed at baseline and at the termination of administration. Volunteers were randomized to receive N-PEP-12 or Placebo in a 2:1 ratio. Thus, 36 study participants received N-PEP-12 and 18 received Placebo.

The primary outcome measure was the Memory Score on the Alzheimer’s Disease Assessment Scale-Cognitive which was obtained by summing scores on the three ADAS-Cog memory tests, the Word Recall, Word Recognition, and Delayed Recall tests. Secondary outcome measures included the Syndrome Kurz Test (SKT), Digit Cancellation Test, Digit Span Subtest from the Wechsler Adult Intelligence Scales, Verbal Fluency test and Sandoz Clinical Assessment Geriatric scale (SCAG) to detect clinical changes in symptomatology.

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A significant difference (p<0.01) favouring N-PEP-12 was found on the primary outcome measure, ADAS-Cog Memory Score. Further, two of the three memory subtests that comprise the score, the Word Recall and the Delayed Word Recall task demonstrated a significant effect of N-PEP-12 (p<0.02) on cognitive performance (Fig 7).

![Differences between N-PEP-12 and Placebo](image)

**Figure 7:** Differences between N-PEP-12 and Placebo on Primary Outcome Measure (ADAS) in total and subtests
Results from the ANCOVA model, **p<0.01, *p<0.05

Table 1 provides a comparison of the two groups on the primary outcome measures, the ADAS Memory Score and the ADAS-Cog subtests.

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome Measure</th>
<th>N-PEP-12 [Mean ± SD]</th>
<th>Placebo [Mean ± SD]</th>
<th>p-value</th>
<th>favors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADAS Memory Score</td>
<td>13.9 ± 0.33</td>
<td>15.5 ± 0.46</td>
<td>0.01</td>
<td>N-PEP-12</td>
</tr>
<tr>
<td></td>
<td>Word Recall</td>
<td>5.0 ± 0.15</td>
<td>5.7 ± 0.22</td>
<td>0.02</td>
<td>N-PEP-12</td>
</tr>
<tr>
<td></td>
<td>Word Recognition</td>
<td>3.3 ± 0.23</td>
<td>2.9 ± 0.33</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed Word Recall</td>
<td>5.6 ± 0.27</td>
<td>6.8 ± 0.38</td>
<td>0.02</td>
<td>N-PEP-12</td>
</tr>
</tbody>
</table>
A unique neuroprotective natural health product to counteract age associated memory impairment

Differences between the two groups were also shown in the secondary outcome measures (Fig 8). More specifically, a significant superiority (p<0.01) of N-PEP-12 over Placebo was seen on the SCAG and the SKT scale. Furthermore, a trend favouring N-PEP-12 was seen on WAIS Digit Span.

![Figure 8: Differences between N-PEP-12 and Placebo on Secondary Outcome Measures](image)

Results from the ANCOVA model, **p<0.01

As to the magnitude of the cognitive effects seen in this study, improvement on the primary outcome measure, the ADAS Memory Score, was over 10% higher among subjects of the N-PEP-12 group than those of the placebo group. If one examines the magnitude of drug effect on the ADAS Delayed Recall Task or the SKT Test it is on the order of 17-18%. So, what is the clinical meaning of a 10% or an 18% improvement when treated with any drug relative to placebo? Cross-Sectional studies\(^{15}\) involving large cohorts at each decade across the life span have yielded estimates of memory loss on word recall and delayed recall tests between age 30 and 70 on the order of 50% (Youngjohn et al, 1991). So, the observed effect size for N-PEP-12 of 17%, could be translated into a reversal of approximately 13 years of memory decline.

N-PEP-12
A unique neuroprotective natural health product to counteract age associated memory impairment

Adverse events reported in each group are shown in Table 2. There were no differences whatsoever between N-PEP-12 and Placebo (p-value = 0.99) and N-PEP-12 appeared to be extremely safe and well tolerated.

Table 2: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N-PEP-12</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation Episode</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Face Dysethesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache Episodes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Submandibular Dysesthesia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Number (%)</strong></td>
<td><strong>8 (22%)</strong></td>
<td><strong>4 (22%)</strong></td>
</tr>
</tbody>
</table>

Results of the study demonstrate that N-PEP-12 is a safe and effective compound for counteracting mild memory deficits that occur so frequently in later life. It is of interest that subjects with N-PEP-12 intake over one month improved relative to subjects with placebo intake both on objective and subjective assessments of memory. Subjects not only performed better on neuropsychological tests but perceived subjective improvement of their mental capabilities and memory performance.
Summary

N-PEP-12 is a unique natural health product which consists of peptone-based neuropeptides. Scientific evidence from experimental studies with N-PEP-12 clearly demonstrates its potent neuroprotective activity and its stimulating effects on synaptic density and neuronal plasticity. These actions are the foundation of N-PEP-12’s beneficial effects on cognitive function and memory performance which have convincingly been demonstrated in human studies.

In placebo-controlled clinical trials, individuals taking N-PEP-12 for one month improved on objective and subjective assessments of memory. They performed better on neuropsychological memory tests and also experienced subjective improvement of their mental capabilities and memory performance. More specifically, N-PEP-12 users in clinical trials have experienced an improvement of short-term memory, their ability to concentrate has increased and they have further reported that they feel more alert and find it easier to learn new information. The observed effects of N-PEP-12 in clinical trials on memory performance and brain bioelectrical activity support its use as natural health product to maintain healthy mental function in humans.

Many memory products claim to have scientific studies supporting their effects but in almost all cases, these studies have been performed with individual components of these products only, often at dosages that are irrelevant to the human use. In contrast, all human studies with N-PEP-12 were conducted with the final product at the dosage that is recommended by the manufacturer.

In conclusion, the studies performed with N-PEP-12 demonstrate that it is an absolutely safe and effective compound for counteracting the cognitive performance decline related to Age Associated Memory Impairment.

N-PEP-12 is the first clinically proven effective memory natural health product.