Safely improving activity and alertness in aging pets

TECHNICAL FILE
A new approach to managing brain aging

Novifit®
(NoviSAMe®)
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SAMe, a molecule naturally present in the body, is well documented for its effects on membrane fluidity, antioxidant cellular activity and the renewal of certain neurotransmitters in the central nervous system.

SAMe has been the subject of much research and many publications in the fields of behavior and geriatrics.

NoviSame is a pure SAMe salt. It is a high quality, stable and active SAMe salt.

Novifit is NoviSame formulated into enteric-coated tablets protected in individually sealed aluminium blister packs.

Long-term stability of the active ingredient has been well documented (3 years).

Helps manage behavioral disorders linked to brain aging in dogs and cats.

Demonstrated effectiveness in placebo-controlled clinical trials among aging dogs with behavioral disorders due to cognitive decline.

Improves levels of activity and memory associated with previously learned tasks.

U.S. patent-pending applications in behavior therapy and geriatrics.

No known drug interactions–ideal for geriatric patients.

Easy once daily administration.*

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*Dogs over 88 lbs receive 1 tablet twice daily.*
Metabolic importance of S-AdenosylMethionine (SAMe)

SAMe: an essential endogenous metabolite

- S-Adenosyl-L-Methionine (SAMe) is a molecule formed by the union of methionine (an amino acid found in food) and ATP (the main energy source in the cell)\(^1\).

- It is found in every living cell and plays a central role in metabolism as a co-factor or precursor in a large variety of biological reactions\(^2\).

- SAMe is able to transfer chemical groups to other molecules in order to facilitate diverse reactions and produce a great variety of compounds that enable the body to function properly.

- Constant de novo synthesis of this compound is required in the body to maintain adequate physiological concentrations\(^1\).

- SAMe is particularly abundant in the brain.

- A deficit of endogenous SAMe has been documented in various pathological situations such as neurological and mood disorders. More generally, a deficit accompanies the process of aging\(^15,31\).
The organism’s use of **SAMe**: three metabolic pathways

**Transmethylation**
- SAMe is the co-factor donor of methyl groups (CH₃) in over 100 different reactions catalyzed by methyltransferase enzymes.
- SAMe transfers its methyl group to diverse substrates including phospholipids, neurotransmitters, proteins and nucleic acids (DNA, RNA). In so doing, it plays a key role in their formation, activation or metabolism.
- **In the brain**, methylation processes dependent upon SAMe are particularly extensive. The products of such reactions include monoamine neurotransmitters, phospholipids and myelin.
- The transmethylation path is particularly important for maintaining the integrity and the fluidity of cellular membranes, required for the organization of surface receptors.
- The methylation of phospholipids increases membranes’ phosphatidylcholine content and thus increases their fluidity. A more fluid environment facilitates the lateral movement of proteins - such as surface receptors - within the lipid bilayer. Intercellular signalling is enhanced (unmasking of receptors).
Processes of methylation dependent on SAMe are also at work in the synthesis and activation of monoamine neurotransmitters, such as noradrenaline, dopamine, and serotonin.\(^5\)

**Transsulfuration**

Once the methyl group has been yielded in the pathway described above, the demethylized SAMe is converted into homocystine, then, after several stages, into various sulphur compounds: cysteine, glutathion, and sulphates.\(^1\)

Glutathione is the major cellular antioxidant that protects tissue from toxins and free radicals.\(^1, 5, 6\)

**Aminopropylation**

SAMe is decarboxylated and its aminopropyl group is transferred to receptor molecules to form polyamines. Methylthioadenosine is produced during this process.

Polyamines play an important role in gene transcription. They influence cell regeneration and repair, through their effects on DNA and cellular replication.\(^1, 5\)

Methylthioadenosine also has anti-inflammatory and analgesic activities.\(^33\)

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**SAMe is essential for supporting the pathways of intermediary metabolism that are particularly affected by the process of aging: protecting cellular membranes, antioxidant activities, renewing neurotransmitters and the mechanisms of cellular regeneration.**
Supporting neuronal membrane functions (methylation path)

Several studies indicate that a methyl group deficit in the central nervous system plays a role in the etiology of Alzheimer’s disease in humans.\textsuperscript{1}

Reduced concentrations of SAMe in cerebrospinal fluid\textsuperscript{18} and in several regions of the brain\textsuperscript{19} have been demonstrated in patients with Alzheimer’s type dementia. Significant changes in the phospholipids that depend on SAMe metabolism have been detected in the brain, using magnetic resonance imagery, during the early stages of Alzheimer’s disease.

Several studies have shown that SAMe improves cognitive function in elderly patients with senile dementia.\textsuperscript{17,28}

Supplementary exogenous SAMe has been shown to be efficacious in restoring the metabolic paths of methylation and thus contributing to maintaining membrane fluidity, unmasking neuronal receptors and enhancing inter-cellular communication.\textsuperscript{1, 29, 30, 32}
SAMe is beneficial when treating neurological disorders linked to age

After repeat doses have been administered for one week, EEG studies revealed that SAMe has a nootropic effect in humans. Nootropic substances (medicines for treating dementia that also stimulate cognitive processes) act to improve intellectual performance and memory among patients with cognitive disorders. In cerebral imaging studies, SAMe was observed to generate it’s most pronounced effect on elderly subjects in a passive, deficient state.15

Furthermore, in clinical studies on depression, it quickly became apparent that elderly patients showed more marked improvement than younger patients.15

Visualizing the effects of SAMe in neuroimagy

The administration of SAMe produces significant effects on cerebral functions in human patients. Topographical data produced by electroencephalogram (EEG) highlights changes typical of classic thymoleptic antidepressants (such as imipramine, amitriptyline, fluvoxamine). Therefore, resulting in the pharmaco-EEG classification of the SAMe nutraceutic substance as an antidepressant.15

Mechanisms

To identify the mechanism behind SAMe’s antidepressant effect, pre-clinical studies point to the fact that it stimulates central monoaminergic neurotransmitters1, 13.

It is also thought that increasing or restoring the methylation of membrane phospholipids plays a role in antidepressant activity. As a methyl donor, SAMe increases cellular membrane fluidity by stimulating the methylation of phospholipids. Increased membrane fluidity is synonymous with increased density of neurotransmitter receptors1,14.
Aging dogs and cats can also suffer from a decline in cerebral functions. The clinical signs commonly associated with brain aging in pets include disorientation, reduced activity, anxiety or irritability, changes in relations with owners, disturbed sleep-wake cycles and housesoiling. 

Non-medical causes of such changes in behavior are linked to degenerative change, chronic hypoxia, damage caused by free radicals, and changes in the concentration of neurotransmitters in the central nervous system. 

Due to SAMe’s mechanism of action, and established applications in human and animal neurology, there is new hope for managing behavioral disorders linked to aging in companion animals.
Pharmacological data on SAMe

Pharmacokinetics of SAMe

Absorption
- After oral administration, SAMe is absorbed into the intestine\(^{24}\). Plasma concentrations show an absorption peak between one and six hours after administration in dogs\(^{23}\). Absorption is faster if the dog has an empty stomach, but plasma concentrations are maintained for longer if SAMe is taken with a meal\(^{33}\).

Distribution in tissues
- Studies carried out with radioactive SAMe [methyl\(^{14}\)C] in humans showed that 60% of radioactivity was incorporated into stable metabolic pools. SAMe is metabolised according to the three metabolic paths described previously. Its methyl group is transferred to cellular compounds that have low turnover rates, such as proteins and phospholipids\(^1,33\). Only 16% and 24% of radioactivity is detected respectively in urine and feces 72 hours after oral administration\(^{32}\).

- SAMe crosses the blood-brain barrier. Concentrations of SAMe in cerebrospinal fluid increase after oral administration\(^1,2\). The compound is involved in several central enzymatic pathways linked to transmethylation and to folate and monoamine metabolism, and in membrane functions of neurotransmission\(^{35,36}\).

Toxicological data on SAMe

Acute and chronic toxicity
- SAMe is classified as a non-toxic compound on the basis of acute, sub-acute and chronic toxicity studies in different animal species\(^{23}\).

- Chronic toxicity studies on rats involving SAMe administered orally at a dose of 200 mg/kg for 104 days did not reveal any impact on food intake, animal weight, blood parameters or the macroscopic appearance of organs.
Pilot study in dogs (internal Virbac study)

- A preliminary clinical trial was conducted by Virbac on 49 dogs of different breeds, all over seven years of age.
- An average dose of 2.5 mg/kg of SAMe was administered in tablet form once a day for 4 months.
- Every month, clinical signs were reviewed and blood analyses carried out.
  - Significant improvements were observed in terms of activity and the propensity to play. Disruption of the sleep-wake cycle and incidences of housesoiling were also reduced.
  - Owners were satisfied with the lack of side-effects and positive results of treatment.
  - Biochemical and hematological parameters revealed no significant changes when compared to basal levels.

Controlled efficacy study in dogs or safety and efficacy trial in dogs (internal Virbac study)

- Tolerance of Virbac’s stable SAMe salt (NoviSame) at the recommended dose of 18 mg/kg was not significantly different from the placebo after uninterrupted daily administration over a period of 2 months during a controlled, multi-center, clinical field trial involving 36 elderly dogs of different breeds.
  - Only one dog receiving SAMEe had a bout of diarrhea at the beginning of the treatment. A temporary change in diet solved the problem without interrupting the treatment.

- During the course of numerous trials, SAMe has proved to be a safe supplement for different species and types of patients to use, notably aging dogs that often present with concomitant organic disorders.
- Most orally-administered SAMe is incorporated into metabolic pools in the organism and not rapidly eliminated. This allows exogenous SAMe to play an important role in molecular transportation. By transferring chemical groups (methyl and sulphur compounds) to other molecules, it produces a great diversity of substances required for the body to function properly.
Novifit and brain aging: an approach founded on proof

Virbac elected to introduce SAMe into the field of brain aging in light of the abundant clinical and experimental data pertaining to this molecule accumulated over the years in relation to psychiatry and neurology in humans and animals.

The aging dog, for example, often presents both physiological and behavioral symptoms that benefit from a SAMe supplement. Signs include behavioral disorders linked to aging (disorientation/confusion, reduced social interaction, disruption of the sleep-wake cycle, housesoiling), which affect the animal’s well being habitus and the quality of its relationship with its owner.

Novifit constitutes a safe element in the treatment of behavioural disorders linked to age in companion animals.

Usage is based on clinical proof generated during an international, multi-center, placebo-controlled trial (presented at the WSAVA Congress in Prague in October 2006 and the AFVAC Congress in Bordeaux in December 2006) illustrating the beneficial effects of the supplement on the quality of life of dogs suffering from the age related behavioral disorders in question.

An exclusive Virbac patent is pending to cover the use of SAMe-based supplements in the treatment of behavioral disorders linked to age in companion animals.

NoviSAMe: an exclusive, pure SAMe salt of pharmaceutical quality

SAMe is a highly reactive molecule; it possesses low intrinsic stability.

It must be protected - in the form of a stable salt, manufactured under extremely strict conditions (low humidity, in a vacuum), then formulated and stored in appropriate galenic form and packaging.

These precautions are indispensable prerequisites for the long-term stability – and therefore efficacy – of the active ingredient in the final product.

To meet these demands, Virbac developed NoviSAMe, a tosylate salt of pure, pharmaceutical-quality SAMe.

NoviSAMe contains 80% of the S,S-isomer of SAMe, the active form of the molecule, and very little of the R,S-isomer (the inactive form).
Novifit: proven stability

- The stability of Novifit has been tested according to VICH international standard methods.
- A batch of Novifit was monitored for 36 months at 25°C and 60% relative humidity.
- The SAMe content of the tablets was determined by HPLC analysis at 0, 3, 6, 12, 24 and 36 months.

The results confirmed the stability of the NoviSAMe in the tablets for three years, highlighting the excellent purity and quality of the product.
Novifit: proven clinical efficacy

Novifit was evaluated as a tool in the management of behavioral disorders linked to age in geriatric dogs in a double blind, placebo-controlled clinical trial in three European countries: Spain, Belgium and France (approved for release at the WSAVA Congress in Prague in October 2006 and the AFVAC Congress in Bordeaux in December 2006).

Veterinarians qualified in behavior therapy and specially trained general practitioners participated in clinical evaluations and the analysis of results.

The results were presented as a scientific communication at the 31st WSAVA Congress (World Small Animal Veterinary Association) held in Prague from October 11-14, 2006.

Accepted for U.S. publication in the peer-reviewed journal, Veterinary Therapeutics.

Equipment and methods

Animals
Thirty-six dogs aged eight and over, of both sexes and various breeds, background and life conditions, were included in the trial. All of the dogs had presented at least two behavioral symptoms from the following list for at least one month: disorientation, confusion/loss of training, lack of vigilance/reduced general activity, reduced social interaction, disturbance of the sleep-wake cycle, occasional house-soiling, anxiety. Exclusion criteria were: an invalidating illness, decompensated cardiac insufficiency, acute renal insufficiency, diabetes, clinical hypothyroidism, hyperadrenocorticism, cancer, any infectious diseases, and the use of psychotropic drugs. None of the study animals were under treatment with psychoactive drugs, pheromones, food or dietary supplement designed to help behavior change by the time of their inclusion in the study. Patients receiving chronic NSAID or DMOA therapy for arthritis could be included in the study, provided their orthopedic condition was stabilized before entering the trial and their analgesic treatment remained unchanged.

Treatments
The dogs were randomly divided into two treatment groups: Novifit (NoviSAMe) or identical placebo tablets. It was impossible to tell the products apart; they were simply identified by batch numbers on the packaging. The tablets were administered daily for two months directly into the animal’s mouth or hidden in a small amount of food. In the group with the active ingredient, the average daily dose of SAMe tosylate was 18.5 mg/kg. All other concomitant therapies to improve behavioral symptoms in the animals were forbidden or discontinued, whether of a pharmacological, food or pheromonal nature. No behavioral therapy instructions were given to owners.

Evaluation
Clinical and behavioral examinations were carried out on Days 0, 30 and 60. A pre-coded grid comprising twelve parameters was completed by the veterinarians on the basis of information provided by the owners. The evaluation addressed disorientation, confusion, loss of training, reduced activity, diminished vigilance, failure to recognize people, deterioration of relationship with owners and other animals in the home, increased proportion of a 24 hour period spent sleeping, house-soiling and displays of anxiety. A score of 0 to 3 was awarded to each parameter according to the observed severity of the disorder.
The scores were then totaled to give a ‘Standardized Geriatric Behavior Score’ (SGBS) reflecting the overall severity of the disorders observed. Parameters linked to the presence of osteoarthritis, locomotor difficulties and pain/stiffness were scored separately in the same way. Furthermore, an ‘inability’ questionnaire specific to each case was developed with owners: between 1 and 4 daily activities judged problematic for the dog on Day 0 were re-evaluated at home every two weeks throughout the duration of the trial. The dog’s ability to perform each of the activities was evaluated on a scale ranging from 0 (no problem) to 3 (impossible). Scores were totaled to give an ‘Individual Specific Inability Score’ (ISIS). Owners gave their opinion on the results of the treatment on Day 60.

Results

Anamnesis
On average, behavioral disorders linked to age commenced at the age of 10.4 years. Specific events preceding the appearance of clinical signs could only rarely be identified: household move, death of another animal in the home, separation from owner and temporary loss of vision were mentioned for some individuals. In most cases, behavioral symptoms were getting worse/becoming more frequent (16 cases) or were progressing slowly (10 cases). A stationary chronic state was reported in the 10 other cases. Associated behavioral disorders included separation anxiety (1 case), fear of storms (1 case), running away (1 case), difficult relationship with owners (1 case) and epilepsy (2 cases). five dogs had already received treatment for geriatric behavioral disorders for longer than one month (vincamine/papaverine, clomipramine or selegiline).

Symptoms on Day 0
The most frequent signs in the animals were relative loss of training (72.2% of subjects), reduced useful activity (75%), lack of reaction to orders/lack of interest/apathy (77.8%) and an overall increase in hours spent sleeping (83.3%). Intermittent signs of anxiety such as apprehension, panting, whimpering and shaking (61.1% of dogs) and agitation, wandering and whining at night (52.8%), were also reported in most cases. Locomotor disorders and pain/stiffness linked to osteoarthritis of moderate intensity were only observed in 27.8% of patients.
The most problematic activities for the dogs, as reported by owners, reflected geriatric behavioral disorders. Deficits were observed in terms of each dog’s propensity to play, to respond or interact with its owner, to act normal during the day and sleep at night, to find its way in a familiar place, to defecate at the right time and in the right place and to remain even tempered.

On Day 0, no significant difference was detected between the treatment groups in terms of SGBS and ISIS scores (Mann-Whitney U tests, P>0.05).

Basal free $T_4$ levels were determined for all of the dogs. The results of only five animals were slightly below normal.

**Evolution of clinical signs during the trial**

A significant drop in the SGBS score was observed in both groups after one month of treatment (Wilcoxon rank tests, statistical difference in relation to Day 0, P<0.0006). However, the reduction was substantially greater in the Novifit (SAMe) group compared to the placebo group (Mann-Whitney U tests between groups, P=0.016 at one month, P=0.037 at two months) (Fig. 1). The average reduction in SGBS score on Day 60 was 44.1% and 24.7% with Novifit and the placebo respectively.

More dogs taking SAMe supplements responded favorably to treatment: 64.7% compared to 36.8% for the placebo group.

**Table 1 – Response to treatment on Day 60**

<table>
<thead>
<tr>
<th>Number (%) of dogs</th>
<th>No response</th>
<th>Acceptable response</th>
<th>Good response</th>
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<tr>
<td>Novifit (SAMe) (n=17)</td>
<td>6 (35.3%)</td>
<td>4 (23.5%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Placebo (n=19)</td>
<td>12 (63.2%)</td>
<td>4 (21%)</td>
<td>3 (15.8%)</td>
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Reduction of SGBS score compared to Day 0: <30% = no response, 30-50% = acceptable response, >50% = good response.
The six dogs that did not respond to the administration of SAMe had histories of signs of anxiety that showed little improvement during the trial. Their initial backgrounds featured more severe chronic behavioral disorders. Only one of those dogs had levels of free $T_4$ below normal.

The average improvement of activity level (57.5%), vigilance (59.5%) and of a certain number of acquired behaviors, notably elimination (57.1%), was clinically significant after two months of using Novifit. On the other hand, improvements obtained during this period were more moderate for signs such as confusion (33.3%) and the global number of hours spent sleeping per day (26.7%).

During the trial, neither of the treatments was observed to have a significant effect on the signs of osteoarthritis.

A significant reduction in the ISIS score was recorded in both groups from month one (Wilcoxon rank test, difference in relation to Day 0, $P<0.003$). Although a placebo effect was detected, Novifit was perceived by owners as effective in improving the most problematic activities for their senior dogs (Mann-Whitney U test between the groups, $P=0.004$ on Day 30, $P=0.013$ on Day 60) (Fig. 2). After two months of treatment, the average reduction in the ISIS score was 49% with Novifit and 23.9% with the placebo.

Ten (58.8%) and four (21.1%) owners were satisfied to very satisfied with the effectiveness of Novifit and the placebo respectively. The main comment from owners pertaining to use of the nutraceutical was the impression of a more active and reactive animal during treatment.

Ease-of-use of tablets administered into the mouth or hidden in a small amount of food was deemed good to excellent by owners in 77.8% of cases.

Tolerance of Novifit was deemed good to excellent by owners for 94.1% of the dogs. One animal had temporary diarrhea during the first days of taking the supplement. It was cleared up quickly without interrupting the treatment by reducing the animal’s food intake.
Conclusion

Under the conditions of a randomized double-blind trial, Novifit proved more effective than the placebo in improving behavioral disorders linked to age in dogs. This SAMe supplement is palliative, permitting moderate to marked improvement in behavioral signs in the majority of cases. The main benefits observed concern stimulation of activity, vigilance and the ability to perform certain acts that have been learned. As a result, the quality of an aging dog’s life improves. These results are in line with clinical data obtained on the use of SAMe in elderly human patients.

A significant placebo effect was observed during the trial, without doubt due to the subjective nature of evaluating the behavioral parameters in question. It reflects the expectations of owners in terms of potential benefits from the supplement under study. However, the magnitude of the effects of Novifit, reflected in this trial by behavioral scores and owner opinions, clearly places the activity of this supplement above that achieved with the placebo.

The effects of a SAMe supplement are progressive in aging dogs. Two uninterrupted months of daily administration resulted in significant clinical improvements. In so far as no significant effect on specific locomotor parameters was detected, increased activity from the dogs does not seem to result from SAMe’s impact on the symptoms of osteoarthritis.

This product is well tolerated in aging dogs. Gastro-intestinal episodes may rarely be observed, as reported in one individual in this field study.
Novifit: practical recommendations

Field of application

Novifit is a nutraceutical intended to help control behavioral disorders related to brain aging:
- It increases vigilance and activity
- It improves relations with the owner
- It regulates sleep cycles
- It reduces housesoiling

Targets

- Species: dogs and cats
- Profiles, practical situations:
  - Animals that demonstrate decreased interest in owner interactions
  - Animals that vocalize and are restless at night (dogs that confuse day with night)
  - Animals that housesoil
  - Animals that are anxious or irritable

Recommended usage

- Three formats for different sizes of animal

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<tr>
<th>Species</th>
<th>Novifit S</th>
<th>Novifit M</th>
<th>Novifit L</th>
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<tr>
<td>Cat</td>
<td>1 tablet a day</td>
<td></td>
<td></td>
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<tr>
<td>Dog &lt;22 lbs (&lt; 10 kg)</td>
<td>1 tablet a day</td>
<td></td>
<td></td>
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<tr>
<td>Dog 22-44 lbs (10-20 kg)</td>
<td>1 tablet a day</td>
<td></td>
<td></td>
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<tr>
<td>Dog 44-88 lbs (20-40 kg)</td>
<td>1 tablet a day</td>
<td></td>
<td></td>
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<tr>
<td>Dog &gt; 88 lbs (&gt; 40 kg)</td>
<td>1 tablet twice a day</td>
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Novifit S for cats and dogs weighing <22 lbs (< 10 kg)
Novifit M for dogs weighing between 22-44 lbs (10 and 20 kg)
Novifit L for dogs weighing >44 lbs (> 20 kg)

Minimum treatment 2 months, renewable. One box of 30 tablets in an aluminium blister pack for longer shelf life.

- Administer tablets for at least two months
  - Prolong if necessary as recommended by the veterinarian
  - In the event of a weak response, the animal must return to the veterinarian
  - Consultation with a behavior specialist can improve results
  - The tablets can be taken with food
  - The tablets should not be broken

Advantages

- Minimal side effects
- Efficacy demonstrated in a multi-center, double-blind, placebo-controlled trial
- Fast results—less than one month
- Improves quality of life and relationship with owner
- Purity of the molecule, unique manufacturing process, long-term stability
- A single daily dose*
- Three presentations (S, M and L)
- No known drug interactions

* Dogs over 88 lbs receive 1 tablet twice daily.
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