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**DENAMARIN®**

Nutramax Labs.

*TWO ACTIVES - ONE PATENTED FORMULA*

Available only from your veterinarian

Denamarin, a patented nutritional supplement for veterinary use Only, combines a pure and stabilized S-Adenosylmethionine with silybin-phosphatidylcholine complex. Denamarin is available in three convenient sizes: Denamarin for Cats and Small Dogs, which contains 90 mg of S-Adenosylmethionine and 9 mg of silybin A+B; Denamarin for Medium Dogs, which contains 225 mg of S-Adenosylmethionine with 24 mg of silybin A+B; and Denamarin for Large Dogs, which contains 425 mg of S-Adenosylmethionine and 35 mg of silybin A+B. As S-Adenosylmethionine is sensitive to moisture, the enteric-coated tablets are individually sealed in specialized moisture-resistant blister packs.

## **BACKGROUND**

S-Adenosylmethionine is an endogenous molecule synthesized by cells throughout the body and is formed from the amino acid methionine and ATP. It is an essential part of three major biochemical pathways: transmethylation, transsulfuration and aminopropylation. As part of these pathways, S-Adenosylmethionine is essential to all cells and is particularly important in hepatocytes because of their central role in metabolism. A deficiency of S-Adenosylmethionine, therefore, may initiate or contribute to abnormalities of cellular structure and function in the liver as well as many other body tissues. Conversely, exogenous administration of S-Adenosylmethionine has been shown to result in improvements in hepatocellular function in both *in vivo* and *in vitro* studies, without cytotoxicity or significant side effects.<sup>1-5</sup> Precursors of S-Adenosylmethionine do not have similar effects. Administration of methionine to animals with decreased liver function may not increase hepatic S-Adenosylmethionine levels and may be toxic.<sup>6</sup> The best way to increase S-Adenosylmethionine levels in the body is by direct supplementation with S-Adenosylmethionine.

Silybin is the most biologically active component of an extract from milk thistle known as silymarin,<sup>7</sup> and its absorption is enhanced by phosphatidylcholine.<sup>8-11</sup> Silybin/silymarin has been shown to have beneficial effects on liver function.<sup>12-14</sup>

## PURPOSE

The combination of S-Adenosylmethionine and silybin in Denamarin provides a multi-faceted approach to liver support.

S-Adenosylmethionine has been shown to increase hepatic glutathione levels in cats and dogs.<sup>1,15</sup> Glutathione is a potent antioxidant that protects hepatic cells from toxins and death. A study found that low liver glutathione concentrations are common in dogs and cats with decreased hepatobiliary function.<sup>16</sup> Denamarin is recommended to improve hepatic glutathione levels in patients to help maintain and protect liver function. Denamarin may also be used in other areas of tissue oxidant injury and RBC fragility caused by certain toxins or drugs which are related to reduced glutathione concentrations.<sup>6</sup> Denamarin's mechanism of action, however, goes beyond increasing glutathione levels, in that S-Adenosylmethionine has also been shown to protect liver cells from cell death<sup>2</sup> and may be useful in cell regeneration.<sup>6</sup> A study has also shown that S-Adenosylmethionine may improve bile flow in cats.<sup>5</sup>

Silybin/silymarin has many different mechanisms of action. *In vitro* and *in vivo* studies have shown that it protects against oxidative stress;<sup>17,18</sup> promotes hepatocyte protein synthesis,<sup>19</sup> a mechanism for liver cell regeneration; inhibits leukotriene production,<sup>20,21</sup> which can be beneficial as production of leukotrienes is a component of the inflammatory response; stimulates biliary flow and production of hepatoprotective bile salts (e.g., beta-muricholate and ursodeoxycholate);<sup>22</sup> and increases levels of glutathione.<sup>23</sup>

In a study, silybin was shown to be protective in acute *Amanita phalloides* mushroom poisoning in dogs, where one-third of the untreated dogs died, while all dogs in the silybin-group lived. Silybin-group dogs also had lower bilirubin, AST, ALT, and ALP levels and improved prothrombin times compared to control dogs.<sup>13</sup> In another report, the liver enzymes improved in five out of six dogs with 30 days of silymarin administration.<sup>14</sup>

## PHARMACOKINETICS

In a pharmacokinetic study with fasted dogs given S-Adenosylmethionine, peak plasma levels were recorded in most dogs within 4 hours of administration.<sup>1</sup> A pharmacokinetic study in fasted cats showed peak plasma levels at 2-4 hours post S-Adenosylmethionine administration.<sup>15,24</sup>

Silybin has low bioavailability.<sup>8</sup> Denamarin, therefore, has been specially formulated to address this issue. It contains silybin in a complex with soybean phosphatidylcholine, resulting in superior absorption and bioavailability compared to silymarin or silybin administration alone.<sup>8-11</sup> A study in dogs showed plasma silybin levels more than four times higher with administration of a silybin-phosphatidylcholine complex (SPC) than the levels obtained with administration of silymarin alone (see figure 1 below).<sup>11</sup> Studies in rats showed that administration of the silybin-phosphatidylcholine complex was capable of reaching effective intracellular levels in liver microsomes not achieved with silybin administration alone.<sup>17</sup>

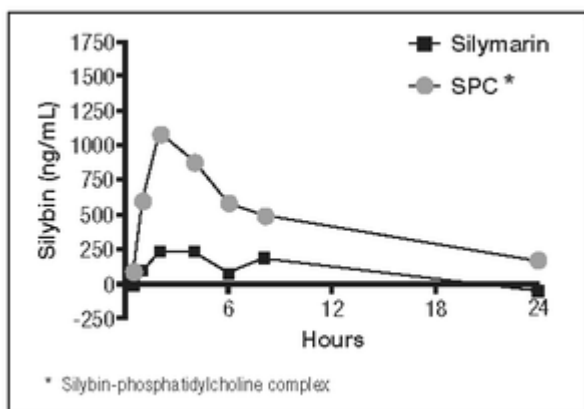


FIGURE 1

Plasma levels in dogs after oral administration of silymarin versus SPC (silybin-phosphatidylcholine complex). Each was given at the same amount based on silybin content (178 mg).<sup>11</sup>

## SAFETY

The ingredients in Denamarin<sup>®</sup> possess exceptionally wide margins of safety. Oral acute toxicity studies in rats indicated an LD<sub>50</sub> greater than 4,640 mg/kg for S-Adenosylmethionine.<sup>6</sup> Clinically healthy dogs administered 20 mg/kg/day of S-Adenosylmethionine for 6 weeks and clinically healthy cats administered S-Adenosylmethionine at 2 times the recommended daily amount for 113 days remained healthy with no adverse effects from the administration.<sup>1,15</sup>

There are no known drug interactions or contraindications to the use of silybin/silymarin in animals.<sup>25,26</sup> While mild side effects, such as gastrointestinal upset, itching and headache, have been rarely reported in primates,<sup>25,27,28</sup> no side effects have been noted in dogs or cats.<sup>11,14,25,26,29,30</sup> The specific silybin-phosphatidylcholine complex in Denamarin has been evaluated in both acute and chronic use safety studies: an acute toxicity study in dogs using levels greater than 80x the amount in Denamarin revealed no adverse physiologic effects,<sup>30</sup> and a chronic toxicity study in monkeys who received greater than 80x the amount in Denamarin for 26 weeks showed no compound-related adverse effects.<sup>27</sup>

## ADMINISTRATION AS A NUTRITIONAL SUPPLEMENT

Please follow the administration charts below as a guide.

### FELINE AND CANINE DENAMARIN DAILY\* ADMINISTRATION GUIDE

#### For Cats and Small Dogs

| Body Weight |           | # Tablets  |
|-------------|-----------|------------|
| Pounds      | Kilograms |            |
| Up to 12    | Up to 5.5 | One tablet |

#### For Medium Dogs

| Body Weight |           | # Tablets  |
|-------------|-----------|------------|
| Pounds      | Kilograms |            |
| 13 to 34    | 6 to 15.5 | One tablet |

#### For Large Dogs

| Body Weight |            | # Tablets    |
|-------------|------------|--------------|
| Pounds      | Kilograms  |              |
| 35 to 65    | 16 to 29.5 | One tablet   |
| 66 to 120   | 30 to 54.5 | Two tablets  |
| Over 120    | Over 54.5  | Three tablet |

\*The number of tablets can be gradually reduced or increased at any time depending on the pet's needs. Many pets are maintained long-term on every-other-day or every-third-day administration.

For optimal absorption, the tablets should be given on an empty stomach, at least one hour before feeding, as the presence of food decreases the absorption of S-Adenosylmethionine. Denamarin can be used in conjunction with Marin<sup>®</sup> to provide additional silybin levels and the benefits of vitamin E and zinc supplementation. If Marin is used in conjunction with Denamarin, the two products should be administered 12 hours apart for best response.

## **STORAGE**

Store in a cool dry place not to exceed 86° F. Keep tablets in original blister pack until used.

Tablets are sensitive to moisture and extreme heat and should not be split or crumbled.

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Any questions or comments?

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NUTRAMAX LABORATORIES, INC., 2208 Lakeside Boulevard, Edgewood, Maryland 21040

02-1014-02

|  |  |            |
|--|--|------------|
| FOR CATS and SMALL DOGS<br>up to 12 lbs. | S-Adenosylmethionine (90 mg) and Silybin A+B (9 mg) - 30 stabilized tablets                      | 01-1026-02 |
| FOR CATS and SMALL DOGS<br>up to 12 lbs. | S-Adenosylmethionine (90 mg) and Silybin A+B (9 mg) - 300 stabilized tablets (Dispensing Size)   | 01-1029-02 |
| FOR MEDIUM DOGS<br>13 to 34 lbs.         | S-Adenosylmethionine (225 mg) and Silybin A+B (24 mg) - 30 stabilized tablets                    | 01-1027-02 |
| FOR MEDIUM DOGS<br>13 to 34 lbs.         | S-Adenosylmethionine (225 mg) and Silybin A+B (24 mg) - 260 stabilized tablets (Dispensing Size) | 01-1030-02 |
| FOR LARGER DOGS                          | S-Adenosylmethionine (425 mg) and Silybin A+B (35 mg) - 30 stabilized                            | 01-1028-   |

|                                     |  |            |
|-------------------------------------|--|------------|
| 35 lbs. and Over                    | tablets  | 02         |
| FOR LARGER DOGS<br>35 lbs. and Over | S-Adenosylmethionine (425 mg) and Silybin A+B (35 mg) - 220 stabilized tablets (Dispensing Size) | 01-1031-02 |

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