COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BOLDO FOLIUM

SUMMARY REPORT

1. *Peumus boldus* is a tall shrub, which grows mainly in Chile and Peru, but is also cultivated in Europe. The medicinal parts are the leaves, *Boldo folium*.

   The crude drug contains 0.25% to 0.5% isoquinoline alkaloids of the aporphine type, main alkaloid boldine and approximately 2% volatile oil, the main components are p-cymene, cineol, ascaridiole, additionally boldoglucin, a glycoside, flavonic compounds (in particular glycosides of rhamnetin,isorhamnetin and kaempferol) and tannin.

2. *Boldo folium* are used in veterinary medicine in the therapy of hepatic dysfunction, cholelithiasis, hepatic congestion, cirrhosis and chronic hepatitis. A powder for oral use to be mixed with the feed or drinking water is given at a daily dose of 20 to 40 mg/kg bw, divided into at least two administrations per day until remission of the symptoms (usually a few days).

   The indications in human medicine are minor hepatobiliary dysfunction, symptomatic treatment of mild digestive disturbances and as an adjuvant in constipation. The daily oral dose in human medicine is 10 to 50 mg boldine/day or 2 to 5 g of the drug as a tea infusion, 0.2 to 0.6 g or the crude drug (or equivalent hydroethanolic extract), 1 to 3 ml/person of the tincture (1:5, ethanol 80%) or 0.5 to 1 ml of a fluid extract.

3. *Boldo folium* extracts show choleretic action (due to the flavons) in humans and dogs, and especially cholagogic action (due to the alkaloid boldine) as well as an increase of urea excretion.

   In dogs operated for biliary fistula *Boldo folium* causes an increase of bile secretion and changes of chemical and physical characteristics of bile. The alkaloid boldine was found to reduce the tonus, to slower the peristaltic and to relax when spastic cramps occur.

   Both a hydroethanolic extract of *Boldo folium* and boldine are hepatoprotective *in vitro* in isolated rat hepatocytes. Boldine inhibits microsomal lipid peroxidation and has *in vitro* antioxidant properties. It also acts as a smooth muscle relaxant by an antagonistic effect on acetylcholine-mediated muscle contractions on isolated rat ileum.

   Other *in vivo* effects of a hydroethanolic extract of *Boldo folium* include protection against carbon tetrachloride induced hepatotoxicity in mice, laxative effect in rats and, after intraperitoneal administration, anti-inflammatory activity in the carrageenan-induced oedema test in rats. Boldine alone was not effective in the latter test system. However, for boldine anti-inflammatory activity in carrageenan-induced paw oedema in guinea pigs (oral ED$_{50}$ 34 mg/kg bw) and anti-pyretic activity in bacterial pyrogen-induced hyperthermia in rabbits (reduction ranging from 51 to 98%) after oral administration of 60 mg/kg bw are reported by a different study group.

   The volatile oil of *Boldo folium*, obtained by hydrodistillation, is reported to have some antibacterial and antifungal activity.

4. No information on pharmacokinetics of *Boldo folium* is available. However, after oral administration of 400 and 800 mg/kg bw of a hydroethanolic extract of *Boldo folium* to rats, detection of boldine in the urine has been reported.
5. Acute toxicity of the main active constituent boldine was tested in mice and guinea pigs. After oral administration of 0.5 g/kg bw and 1.0 g/kg bw of the alkaloid, respectively deaths were observed in mice and guinea pigs. Subcutaneous injection of 0.25 g/kg bw and 0.5 g/kg bw, respectively, led also to deaths. After oral administration of a hydroethanolic extract (1:1) of *Boldo folium* to mice, an LD$_{50}$ of about 6 g/kg bw was observed.

6. No data on repeated dose toxicity of *Boldo folium* or preparations thereof are available.

7. No data on mutagenicity and carcinogenicity of *Boldo folium* are available. Boldine showed no mutagenic activity *in vitro* in the *Salmonella*-microsomal assay, strains TA100, TA98 and TA102 (up to 200 µg), in the SOS chromotest in *Escherichia coli* (up to 10 µg boldine), and in *Saccharomyces cerevisiae* (up to 200 µg). Boldine also did not induce a statistically significant increase in the frequency of chromosome aberrations or sister chromatid exchanges *in vitro* in human peripheral lymphocytes (up to 40 µg/ml) or *in vivo* in mouse bone marrow cells (up to 900 mg/kg bw orally).

8. No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages in human medicine. Signs of paralysis are reported to appear following intake of very high dosages. A case is described in the older scientific literature in which depression, colour and sound hallucinations as well as partial motoric aphasia occurred following the consumption of boldine over a period of months.

**Conclusions and recommendation**

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of *Boldo Folium* in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- *Boldo folium* is used in a small number of individual animals, for infrequent and for non-regular treatments,
- treated animals are unlikely to be sent for slaughter during or immediately after treatment,
- *Boldo folium* are of low acute oral toxicity;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Boldo folium* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boldo folium</em></td>
<td>All food producing species</td>
<td></td>
</tr>
</tbody>
</table>