European Medicines Agency
Evaluation of Medicines for Human Use

London, 14 January 2009
Doc. Ref.: EMEA/HMPC/591131/2007

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

ASSESSMENT REPORT ON *PEUMUS BOLDUS* MOLINA, FOLIUM

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	January 2008 March 2008 May 2008 November 2008 January 2009
ADOPTION BY HMPC	14 January 2009

KEYWORDS	Herbal medicinal products; HMPC; Community herbal monograph; traditional use; *Peumus boldus* Molina; Boldi folium; boldo leaf

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I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

II. ASSESSMENT REPORT FOR *PEUMUS BOLDUS* MOLINA, FOLIUM WITH TRADITIONAL USE

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Peumus boldus* Molina, folium (Whole or fragmented, dried leaf)
Herbal preparation(s)	Comminuted herbal substance Dry extract (5:1, aqueous)
Pharmaceutical forms	Herbal substance or herbal preparations for oral use as herbal tea or in solid dosage forms.
Rapporteur	Linda Anderson

II.1 INTRODUCTION

II.1.1 Description of the herbal substance

Boldo leaf (Boldi folium) consists of the whole or fragmented dried leaf of *Peumus boldus* Molina. It contains not less than 0.1% of total alkaloids, expressed as boldine ($C_{19}H_{21}NO_4$ = 327.4), calculated with reference to the anhydrous drug. [European Pharmacopoeia]

Boldo leaf contains 2-4% of volatile oil. Major constituents reported as: ascaridole (16-38%), 1,8 cineole (11-39%) and *p*-cymene (9-29%) (Bradley, 2006).

Ascaridole is highly toxic (see Section II.2.3.1) and this raises concerns about the suitability of boldo leaf in traditional herbal medicinal products.

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

Peumus boldus Molina (Monimiaceae) is an evergreen shrub or small tree indigenous to Chile and Peru. A detailed review on the pharmacognosy of *P. boldus* has been given by Schindler (Schindler, 1957).

The dried leaves have been reported in medicinal usage since the 19th century in South America against diseases of the liver and gallstones. In 1870, the leaves of *Peumus boldus* are reported to have been introduced in Europe and first described by Bourgoin and Verne (Lanhers *et al*., 1991).
Pharmacognostical texts, pharmacopoeias and handbooks list the therapeutic uses as cholagogue, choleretic, digestive disturbances, diuretic, hepatic stimulant, stomachic, sedative and anthelmintic (Grieve, 1931; British Herbal Compendium, 1992; British Herbal Pharmacopoeia, 1976; British Pharmaceutical Codex, 1934; The Complete German Commission E Monographs, 1998; ESCOP, 2003; Hansel, 1991; Martindale Extra Pharmacopoeia, 1924; Potter's New Cyclopedia 1973; Benedum *et al,* 2006). Boldo leaf has also been reported as used for the treatment of headache, earache, toothache, rheumatism and urinary tract inflammation (Spiesky and Cassels 1994).
Cholagogues and choleretics are well known in traditional herbal medicine: cholagogues are reported to stimulate the release of bile that has already formed in the biliary system whilst choleretics stimulate bile production by hepatocytes (Mills and Bone, 2000; Schulz *et al.,* 1998).

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding boldo leaf and the major alkaloid, boldine.

<u>Constituents</u> (Barnes *et al*., 2007; Bradley, 2006; ESCOP, 2003; Leung, 1996; Wichtl, 2004)

<u>Alkaloids</u>

Isoquinoline-type 0.25-0.7%. Boldine, isoboldine, 6a,7-dehydroboldine, isocorydine, isocorydine-*N*-oxide, norisocorydine, laurolitsine, laurotetanine, N-methyllaurotetanine, reticuline, (-)-pronuciferine, sinoacutine.

Boldine is usually the major alkaloid (reported as 14-36% of total alkaloids). However, some sources of leaf are reported to have boldine as a minor alkaloid (0.28-0.32% total alkaloids) (Bradley, 2006).

Flavonoids: flavonols (e.g. isorhamnetin) and their glycosides.

Volatile oil: 2.0-2.6% (Vogel *et al* 1999). Major constituents reported as: ascaridole (16-38%), 1,8 cineole (11-39%) and *p*-cymene (9-29%) (Bradley, 2006).

Vogel *et al.* 1999 have shown that the principal components of the oil are determined genetically and have reported levels: ascaridole (34.6%), *p*-cymene (3.9%), 1,8-cineole (0.5%). Other constituents include: α-pinene, camphene, β-pinene, sabinene, Δ^3-carene, terpinolene, limonene, γ-terpinene, , 2-nonanone, fenchone, 1-methyl-4-isopropenylbenzene, camphor, , α-fenchol, terpinen-4-ol, α-terpineol and methyl eugenol (Opdyke, 1982).

Other constituents: coumarin, resin, tannin.

Choleretic effects – studies with boldo leaf extracts

Early studies in rats have reported choleretic effects with extracts of boldo (full details not available) (Bohm, 1959; Pirtkien *et al*., 1960; Borkowski *et al*., 1966; Levy-Appert-Collin and Levy, 1977).

Subsequent experiments in rats, however, failed to demonstrate choleretic activity after oral administration of 400 or 800 mg/kg aqueous ethanolic extract, intraduodenal administration of 200 or 800 mg/kg, or after intravenous administration of a dry ethanolic extract (4:1) corresponding to boldo leaf at 125- 500 mg/kg (Lanhers *et al*., 1991).

Laxative effect: studies with boldo leaf extracts

A laxative effect has been reported in rats following oral administration of a hydroethanolic extract at 400 or 800 mg/kg daily for 8 weeks (Magistretti, 1980).

Spasmolytic effect: studies with boldine

Boldine had a concentration-dependent smooth muscle relaxing effect on the acetylcholine-induced contraction of isolated rat ileum via a competitive antagonist mechanism (Speisky *et al*., 1991a).

Antioxidant activity: studies with boldo leaf extracts and boldine

A large number of studies have been carried out on boldo extracts and isolated boldine showing potent free radical-scavenger and antioxidant activity. These studies have been reviewed in detail (O'Brien *et al.,* 2006).

A hydroethanolic extract (corresponding to 0.5 and 1 mg of dried leaf per ml) and boldine (33 µg/ml) showed a hepatoprotective effect against *tert*-butyl hydroperoxide-induced hepatotoxicity in isolated rat hepatocytes (Lanhers *et al*., 1991).

Antioxidant activity: studies with boldine

Boldine inhibited rat liver microsomal lipid peroxidation by 50% at a concentration of 0.015 mM (Cederbaum *et al*., 1992).

Boldine inhibited the peroxidative (accumulation of thiobarbituric acid reactive substances) and lytic damage (trypan blue exclusion and lactate dehydrogenase leakage) to isolated rat hepatocytes induced by *tert*-butyl hydroperoxide (Bannach *et al*., 1996).

Boldine concentration-dependently prevented the haemolytic damage induced by the free radical initiator 2,2'-azobis-(2-amidinopropane)(AAPH) (Jimenez *et al*., 2000).

Boldine reduced the lethal effect induced by stannous chloride on the survival of *Escherichia coli* cultures. In addition, the structural confirmation of the plasmid pUC 9.1 was not

modified by stannous chloride in the presence of boldine. These effects were considered to be due to the antioxidant activity of boldine (Reiniger *et al*., 1999).

The antioxidant properties of boldine have been demonstrated by the prevention of rat brain homogenate autoxidation, the 2,2'-azobis-(2-amidinopropane)(AAPH)-induced lipid peroxidation of red cell plasma membranes and the AAP-induced inactivation of lysozyme. These results indicate that boldine acts as an antioxidant in biological systems susceptible to free radical-mediated reactions (Speisky *et al*., 1991b).

Boldine prevented the ferric-ATP catalysed peroxidation of human liver microsomes and inactivation of cytochrome P450E1 (Kringstein and Cederbaum, 1995).

Anti-inflammatory effects: studies with boldo extracts

An aqueous alcoholic extract showed anti-inflammatory activity in the rat-paw carrageenann-induced oedema test following intraperitoneal administration but boldine was negative in the test at doses of 10 and 20 mg/kg (Lanhers *et al*., 1991, 1992).

Anti-inflammatory effects: studies with boldine

Oral administration of boldine was shown to exhibit a dose-dependent anti-inflammatory activity in the rat-paw carrageenann-induced oedema test with an ED_{50} of 34 mg/kg (Backhouse *et al*., 1994).

Intrarectal administration of boldine (100 mg/kg) to rats with colitis resulted in significantly reduced colonic neutrophil infiltration. Boldine also protected against acid-induced oedema as shown by decreased total colon weight (Gotteland *et al*., 1997).

Antipyretic effects: studies with boldine

Oral administration of boldine (60 mg/kg) was shown to reduce bacterial pyrogen-induced hyperthermia in rabbit (Backhouse *et al*., 1994).

II.2.1.2 Assessor's overall conclusions on pharmacology

Most investigations have been carried out using the isolated alkaloid, boldine. Limited information is available on herbal preparations of boldo leaf and where studies have been reported, details of the preparations are usually lacking. The choleretic effects of boldo leaf have not been confirmed.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding boldo leaf and the major alkaloid, boldine.

Studies with boldo extracts

Boldine was found in the urine of rats after oral administration of a hydroethanolic extract (no further details recorded) of boldo at 400 and 800 mg/kg (Magistretti, 1980)**.**

Studies with boldine

In vitro experiments

Addition of boldine at 200 µM to a suspension of isolated rat hepatocytes was followed by a time-dependent disappearance of boldine from the extracellular medium and accumulation within the cells. Boldine was also concentration-dependently removed from the extracellular medium when boldine was portally perfused through isolated rat livers (Jimenez and Spiesky, 2000).

In vivo experiments

Absorption of boldine was rapid following oral administration to rats at 25, 50 or 75 mg/kg with maximum plasma concentration reached within 15-30 minutes. Boldine was found to be preferentially concentrated in the liver (Jimenez and Spiesky, 2000).

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

Limited data are available on pharmacokinetics.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding boldo leaf and the major alkaloid, boldine

Single/repeat dose toxicity: studies with boldo extracts

Oral administration of a hydroethanolic extract (no further details recorded) of boldo to rats in single doses up to 3 g/kg body weight caused no deaths or toxic symptoms (Magistretti, 1980).

The intraperitoneal LD_{50} in mice of an ethanolic extract of boldo (80%; no further details recorded) was found to be equivalent to 6 g/kg (Levy-Appert-Collin and Levy, 1977).

Oral administration of a dry ethanolic extract of boldo (92.8%; no further details recorded) or of boldine to rats daily for 90 days at 200 mg/kg/day caused significant reductions in blood levels of cholesterol, aspartate aminotransferase (AST), total bilirubin, glucose and urea, although cholesterol and AST were raised after 30 and 60 days. There were no significant changes in creatinine levels. Doses of 50 mg/kg/day did not produce any significant changes over the 90-day period. Neither the boldo extract nor boldine caused any overt signs of toxicity in the heart or kidneys but steatosis was observed in two animals at doses of 800 mg/kg (De Almeida *et al*., 2000).

Single/repeat dose toxicity: studies with boldine/total alkaloids

When boldine was administered orally, doses of 500 and 1000 mg/kg were required to cause death of mice and guinea pigs, respectively (Kreitmar, 1952).

The intraperitoneal LD_{50} values of total alkaloids and of boldine in mice were reported to be 420 and 250 mg/kg, respectively (Levy-Appert-Collin and Levy, 1977).

Total alkaloids from boldo administered by sub-cutaneous injection to dogs produced vomiting, diarrhoea and epileptic symptoms with recovery after 50 minutes (Kreitmar, 1952).

Genotoxicity: studies with boldo extracts

No studies were located using herbal preparations of boldo leaf.

Genotoxicity: studies with boldine

Boldine did not show genotoxic activity in the SOS chromotest with *Escherichia coli* or in the Ames test using *Salmonella typhimurium* strains TA100, TA98 and TA102. Furthermore, it did not induce point and frameshift mutations in haploid *Saccharomyces cerevisiae* cells. Boldine did, however, induce mitotic recombinational events in diploid yeast cells and cytoplasmic 'petite' mutation in haploid yeast cells (Moreno *et al*., 1991).

Boldine did not induce a statistically significant increase in the frequency of chromosome aberrations or sister-chromatid exchanges when tested *in vitro* on human peripheral blood lymphocytes or *in vivo* using mouse bone marrow cells (Tavares and Takahashi, 1994).

Boldine administered intra-peritoneally at sub-lethal doses induced no signs of genotoxicity in mouse bone marrow as assessed by the micronucleus test (Spiesky and Cassels, 1994).

Carcinogenicity

No studies were located using herbal preparations of boldo leaf or boldine.

Reproductive and development toxicity: studies with boldo extracts and boldine

Pregnant rats treated orally with a dry ethanolic extract of boldo (92.8%; no further details recorded) or with boldine at 500 or 800 mg/kg body weight on days 1-5 or days 7-12 of pregnancy showed anatomical alterations in the fetus at the higher dose. Incidents of blastocystotoxic-antizygotic action and a few cases of abortion were also observed in both treated groups at 800 mg/kg body weight. Daily doses of 500 mg/kg body weight did not produce teratogenic or abortifacient activity but reduced fetal weight by 28-40%. The authors concluded at 800 mg/kg/day the boldo extract and boldine had adverse effects at the beginning of egg production and also during implantation (De Almeida *et al*., 2000).

Toxicity of boldo leaf volatile oil

Boldo leaf is reported to contain 2-4% of volatile oil. The major components are ascaridole (16-38%), 1,8 cineole (11-39%) and *p*-cymene (9-29%) (Bradley, 2006).

Boldo leaf oil is stated to be one of the most toxic oils due to the presence of ascaridole (Tisserand, 1995) and the oil should not be used internally or externally.

Ascaridole is a bicyclic monoterpene with a bridging peroxide functional group. It is the main constituent (90%) of Chenopodium oil (*Chenopodium ambrosioides* L., American Wormseed oil) and renders this oil one of the most toxic known. Chenopodium oil has been used in the past as an anthelmintic but has been superseded by safer treatments. The anthelmintic activity is due to the ascaridole content.

Acute toxicity boldo oil

An acute oral LD_{50} value for boldo oil has been given as 0.13 g/kg body weight in rats, with doses of 0.07 g/kg causing convulsions (Opdyke, 1982). The acute dermal LD_{50} in rabbits was between 0.625 and 1.25 g/kg.

Toxicity of Chenopodium oil

Human toxicity and fatal poisoning have been reported with Chenopodium oil (Opydyke 1982). Toxic effects include skin and mucous membrane irritation, headache, vertigo, nausea, vomiting, constipation, tinnitus, temporary deafness, diplopia and blindness, transient stimulation followed by depression of the CNS leading to delirium and coma, occasional convulsions, circulatory collapse due to vasomotor paralysis and sometimes pulmonary oedema. Chenopodium oil is also toxic to the kidneys, liver and haematuria, albuminuria and jaundice have been observed. Several cases of fatal poisoning have been reported in children.

In view of the known toxicity, boldo oil should not be used internally or externally. Where boldo leaf is used, the total exposure to ascaridole should be considered from a safety standpoint. The levels in herbal preparations and herbal medicinal products should be quantified.

II.2.3.2 Assessor's overall conclusions on toxicology

Most investigations have been carried out using boldine. Limited information is available on herbal preparations of boldo leaf and where studies have been reported, details of the preparations are usually lacking. There are no reported genotoxicity or carcinogenicity studies with herbal preparations of boldo leaf. Abortifacient and teratogenic effects in rats were observed with high doses of a dry ethanolic extract and boldine.

In view of the known toxicity, boldo oil should not be used internally or externally. Where boldo leaf is used, the total exposure to ascaridole should be considered from a safety standpoint. The levels in herbal medicinal products should be quantified. No data was located comparing levels of ascaridole in preparations derived from boldo leaf. In view of the low solubility of ascaridole in water the use of aqueous extracts including herbal tea could be accepted. However, the levels of ascaridole in the herbal preparations and herbal medicinal products should be quantified. The use of ethanolic extracts of boldo leaf is not considered acceptable for traditional herbal medicinal products in view of the potentially higher levels of the toxic ascaridole constituent.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

No data available.

II.3.1.1 Pharmacodynamics

Twelve healthy volunteers treated daily with either 2.5 g of a dry extract of boldo (ethanol 60% v/v) containing 0.4% of total alkaloids and 0.12% of boldine showed prolongation of intestinal transit time compared to placebo (Gotteland *et al*., 1995).

Assessor's overall conclusions on pharmacodynamics

Due to lack of data no conclusions can be drawn**.**

II.3.1.2 Pharmacokinetics

No data available.

Assessor's overall conclusions on pharmacokinetics

Due to lack of data no conclusions can be drawn.

II.3.2 Clinical Efficacy

No clinical studies were located with mono-preparations containing boldo. Therefore it is concluded that there are no data to support boldo as a well-established medicinal product with recognised efficacy and acceptable safety.

The following traditional uses have been recorded for boldo leaf:

A Modern Herbal (Grieve, 1931)
Medicinal action and uses: Tonic, antiseptic, stimulant. Useful in chronic hepatic torpor. The oil in 5-drop doses has been found useful in genitor-urinary inflammation. Tincture of boldo used as a diuretic.
Dosage: Tincture of boldo BPC, 10-40 minims (0.6-2.4 ml). Duration of use: No information.

The Complete German Commission E Monographs (Blumenthal, 1998).
Mild spasmodic disorders of gastrointestinal tract; dyspeptic complaints.
Daily oral dose: 3 g. Equivalent amount of preparations. Duration of use: No information.

*Herbal Medicine. Expanded Commission E Monographs (*Blumenthal, 2000).
Dosage: Unless otherwise prescribed: 3 g per day of cut herb.
Infusion: 3 g in 150 ml water. Fluid extract 1:1 (g/ml): 3 ml. Tincture 1:5 (g/ml): 15 ml.
Duration of use: No information.

British Herbal Compendium (Bradley, 1992)
Actions: Choleretic, liver stimulant, hepatoprotective, anti-inflammatory, mildly laxative, antimicrobial. Increases secretion of gastric juice and stated to be diuretic, urinary tract antiseptic and sedative.
Traditional uses: Mild spasmodic disorders of the gastrointestinal tract, especially functional disorders of the bile duct, gall-stones, liver or gall bladder pains, dyspeptic complaints, urinary tract inflammation including cystitis, rheumatism.
Dosage:

British Herbal Pharmacopoeia: Three times daily: dried leaf, 60-200 mg, or as an infusion; liquid extract (1:1 in 45% alcohol) 0.1-0.3 ml; tincture (1:10 in 60% alcohol) 0.5 – 2 ml.
Germany: Daily dose: dried leaf 3 g; 1-2 g as infusion in 150 ml water 2-3 times daily.

British Herbal Pharmacopoeia (1976)
Gall-stones, Pain in liver or gall bladder. Cystitis. Rheumatism. Specific: Cholelithiasis with pain.
Dosage: (3 times daily): 0.25-1 g (powder or infusion); 0.5-1 ml liquid extract (1:1 in 25% alcohol); 0.5-2 ml tincture (1:8 in 45% alcohol). Duration of use: No information.

British Pharmaceutical Codex (1934)
Boldo possesses diuretic and stimulant properties. Leaves are employed in Chile and other South American countries for chronic hepatic congestion and as an aromatic tonic and diuretic in gonorrhoea, and in cystitis and other bladder affections. Boldo leaf is principally used as a diuretic and supposed liver stimulant.
Dosage: Tincture of boldo 1:10 in 60% alcohol, 0.6-2 ml. Duration of use: No information.

Encyclopedia of common natural ingredients (Leung, 1980)
Reported to have choleretic, diuretic, stomachic and cholagogic properties.
Daily oral dose: No information. Duration of use: No information.

ESCOP Monograph (2003)
Minor hepatobiliary dysfunction, symptomatic treatment of digestive disturbances.
Daily dose: 2-5 g of the drug as a tea infusion.
0.2-0.6 g of the drug or equivalent hydroethanolic extract.
Tincture (1:5, ethanol 80% v/v) 1-3 ml.
Fluid extract (1:1 ethanol 80% v/v) 0.5-1 ml.
Duration of use: not more than 4 weeks.

Médicaments à base de plantes (Ministère de la Santé et de L'action Humanitaire, 1990)
Traditionally used to facilitate urinary and digestive elimination functions. Traditionally used as a choleretic or cholagogue.
Daily oral dose: No information. Duration of use: No information.

French Pharmacopoeia 8th edition 1965; 9th edition 1979
Boldo tincture (1:5, ethanol 80% v/v) 1-3 ml.
Fluid extract (1:1 ethanol 80% v/v) 0.5-1 ml.

Handbook of Medicinal Herbs (Duke, 2002)
Leaves used as a mild diuretic especially in liver complaints like jaundice. Also stated to be anodyne, antiseptic, choleretic, hepatotonic, hypnotic, stimulant, tonic and vermifuge. Used for dyspepsia, gout, hepatosis, rheumatism, syphilis and worms. Infusion of leaves used for stomach and liver troubles.
Daily oral dose: 2 – 8 g. Duration of use: No information.

Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004)
Primarily used as a cholagogue.
Daily dose: 1-2 g as infusion in 150 ml water 2-3 times daily.
Duration of use: No information.

Herbal Medicines. A guide for healthcare professionals (Barnes *et al*., 2007)
Stated to possess cholagogue, liver stimulant, sedative, diuretic, mild urinary demulcent, and antiseptic properties. Used for mild digestive disturbances, constipation, gall-stones, pain in liver or gall bladder, cystitis, rheumatism and specifically cholelithiasis with pain.

Martindale Extra Pharmacopoeia (1924)
For dyspepsia, liver affections, rheumatism and as a diuretic for atony of the bladder.
Dosage: Dried leaf: 0.06-0.18 g; Tincture (1 in 5) 90% alcohol: 0.6 –1.2 ml.
Duration of use: No information.

Martindale Extra Pharmacopoeia (1941)
For dyspepsia, liver affections, rheumatism and as a diuretic for atony of the bladder.
Dosage: Dried leaf: 0.06-0.18 g; Tincture (1 in 10) 60% alcohol: 0.6 – 2 ml.
Duration of use: No information.

Martindale Extra Pharmacopoeia (1967)
Boldo is employed in herbal medicine as a diuretic, for hepato-biliary disorders and for gastrointestinal disorders such as constipation.
Dosage: Single dose: liquid extract (1 in 1): 0.5-1 ml; tincture (1 in 5): 0.5-2 ml.
Duration of use: No information.

Potter's New Cyclopedia of Botanical Drugs and Preparations (1973)
Boldo is used as a cholagogue, liver stimulant and diuretic; used for the treatment of gall-stones and cystitis and as an aid to slimming.
Dosage: Liquid extract (1:1) 0.5 – 2ml. Duration of use: No information.

II.3.2.1 Assessor's overall conclusions on the traditional use

Traditional medicinal use of, *Peumus boldus* Molina leaf, in the form of powdered herbal drug, herbal tea or ethanolic extracts is well documented in a number of bibliographic sources for mild digestive disturbances which would be suitable for self- medication. The requirement of medicinal use for at least 30 years (including at least 15 years within the Community) according to Directive 2004/24/EC is considered fulfilled.

The following indication, in accordance with the Commission E monograph is considered acceptable for traditional registration subject to appropriate contra-indications, warnings etc.:

Traditional herbal medicinal product for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.

In view of the potential presence in herbal preparations and herbal medicinal products of the toxic ascaridole constituent, only herbal teas and aqueous extracts are considered acceptable.

However, the levels of ascaridole in the herbal preparations and herbal medicinal products should be quantified.

The use of ethanolic extracts of boldo leaf is not considered acceptable for traditional herbal medicinal products in view of the potentially higher levels of the toxic ascaridole constituent.

II.3.2.2 Dose response studies/duration of use

There are no dose response studies available.

Duration of use:

Limited information is available. Continuous long-term use is not recommended in some sources (Hansel, 1991; Blumenthal, 2000). Based on the German Commission E monograph, boldo leaf preparations should not be taken for more than 2 weeks. If the symptoms persist for more than 2 weeks, a doctor or a qualified health care practitioner should be consulted.

II.3.2.3 Clinical studies (case studies and clinical trials)

There are no studies reported with single ingredient products containing boldo leaf.

II.3.2.4 Clinical studies in special populations (e.g. elderly and children)

None reported.

II.3.2.5 Assessor's overall conclusions on clinical efficacy

There are no clinical investigations with single ingredient products containing boldo leaf.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

No data available.

II.3.3.2 Adverse events

No data available.

II.3.3.3 Serious adverse events and deaths

None reported. **See II.3.3.5.1.**

II.3.3.4 Laboratory findings

No data available.

II.3.3.5 Safety in special populations and situations

No data available. Use in children and adolescents is not recommended because data are not sufficient and medical advice should be sought.

Boldo leaf is contraindicated where there is obstruction of the bile duct, severe liver diseases. Medical advice is recommended in cases of gall-stones (Blumenthal, 2000; ESCOP, 2003).

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

Limited data available. One case report of anaphylaxis following intake of a boldo leaf infusion has been located (Monzon *et al*., 2004). The patient, who had a history of allergic rhinoconjunctivitis related to grass pollen suffered an acute and generalized urticaria, facial angioedema, dysphagia, dysphonia and dyspnea. The reaction was confirmed by positive oral challenge. Hypersensitivity to boldo leaf should be included as a contraindication.

II.3.3.5.2 Drug interactions

Limited data available. A single case report has been located of a potential interaction between warfarin and two herbal products resulting in an increase in INR (Lambert and Cormier, 2001). The herbal products were a liquid preparation of boldo leaf (no details provided) and capsules containing Fenugreek (no details provided). The INR returned to normal once the patient stopped taking the herbal products. No information is available using the individual products thus it is not possible to conclude if only one or both products contributed to the increased bleeding time.

II.3.3.5.3 Use in pregnancy and lactation

No data available. Most sources recommend contra-indication in pregnancy and lactation.
Tests on reproductive toxicity have been performed with a dry ethanolic extract of boldo leaf and boldine administered orally to pregnant rats. Results showed anatomical alterations in the fetus and a few cases of abortion at high doses (see section II.2.3.1).

Safety during pregnancy and lactation has not been established. In view of the findings in the studies on reproductive toxicity , use during pregnancy and lactation should be avoided.

II.3.3.5.4 Overdose

Limited data available. One source reports emetic effect and spasms with very high doses (Braun, 1981).

II.3.3.5.5 Drug abuse

No data available.

II.3.3.5.6 Withdrawal and rebound

No data available.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

No data available.

II.3.3.6 Assessor's overall conclusions on clinical safety

Limited data are available. Use in children and adolescents is not recommended because the available data are not sufficient and medical advice should be sought. boldo leaf should be avoided during pregnancy or lactation. Use is contraindicated where there is obstruction of the bile duct, cholangitis, or liver disease. Medical advice is needed in cases of gall-stones or other biliary disorders. Duration of use should be limited to 2 weeks and if symptoms persist medical advice should be sought.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Sufficient data are available to develop a Community herbal monograph on the traditional use of *Peumus boldus* Molina, folium provided the indications are suitable for self-medication. The proposed indications are in accordance with the Commission E monograph (Blumenthal, 2000):

Traditional herbal medicinal product for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.

Duration of use should be limited to 2 weeks.

Use of boldo leaf is not recommended in children and adolescents and should be avoided during pregnancy and lactation. Boldo leaf is contra-indicated where there is obstruction of

the bile duct, cholangitis liver disease, gallstones or any other biliary disorder that would require medical supervision.
The use of comminuted herbal substance as such and of ethanolic extracts of boldo leaf are not considered acceptable for traditional herbal medicinal products in view of the potential risks associated with the toxic ascaridole constituent.

As the minimum required data on mutagenicity (Ames' test) are not available for herbal preparations of boldo leaf, an inclusion to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.