



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Cinnamomum verum* J. S. Presl, cortex and corticis aetheroleum

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cinnamomum verum</i> J. S. Presl, cortex and corticis aetheroleum
Herbal preparation(s)	a) Comminuted herbal substance b) Liquid extract (DER 1:1) extraction solvent: 70% ethanol c) Tincture (ratio of herbal substance to extraction solvent 1:5) extraction solvent 70% ethanol d) Essential oil obtained by steam distillation from the cortex
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparation in liquid dosage forms.
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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)
  1. *Cinnamomum verum* J. S. Presl. (= *Cinnamomum zeylanicum* Nees), dried bark, freed from the outer cork and the underlying parenchyma (ESCOP, 2003; European Pharmacopoeia 6.2, 2009).
  2. *Cinnamomum verum* J. S. Presl. is also known by the synonym *Cinnamomum zeylanicum* Blume and is member of *Lauraceae* family (Keller *et al.*, 1992).

This assessment report does not evaluate *Cinnamomum aromaticum* Nees (synonym: *Cinnamomum cassia* Blume), cortex although they are both comparable in composition and widely used in flavouring agents in foods and in pharmaceutical and cosmetic preparations (Kommission E, 1990; Barnes *et al.*, 2007).

The drug consists of the dried bark, freed from the outer cork and the underlying parenchyma, of the shoots grown cut stock of *Cinnamomum verum* J. S. Presl. The matt pieces of bark, 0.2-0.7 mm thick (in the form of single or double compound quills) are light brown on the outside and somewhat darker on the inside. The surface is longitudinally striated and the fracture is short and splintery. It contains not less than 12 ml/kg essential oil obtained by steam distillation. It has a characteristic and pleasantly aromatic odour. Its taste is pungently spicy, somewhat sweet and mucilaginous, and only slightly sharp (Bisset, 1994).

Cinnamon bark contains up to 4% of essential oil consisting primarily of cinnamaldehyde (60-75%), cinnamyl acetate (1-5%), eugenol (1-10%) (WHO Vol. 1, 1999),  $\beta$ -caryophyllene (1-4%), linalool (1-3%) and 1.8-cineole (1-2%) (ESCOP, 2003).

Other constituents are oligopolymeric procyanidins, cinnamic acid, phenolic acids, pentacyclic diterpenes cinnzeylanol and its acetyl derivative cinnzeylanine and the sugars mannitol, L-arabino-D-xylanose, L-arabinose, D-xylose,  $\alpha$ -D-glucane as well as mucilage polysaccharides (Hänsel *et al.*, 1992; ESCOP, 2003).

The essential oil of the bark is described in the European Pharmacopoeia (6.2, 2009).

There exists a summary report on the essential oil of cinnamon bark by the Committee for Veterinary Medicinal Products. According to this information, the oil mainly contains cinnamaldehyde (55-76%), eugenol (5-18%) and saffrole (up to 2%). This document refers also to human use (CVMP 2000).

Cinnamon bark oil may be adulterated with cinnamon leaf oil and oil of cassia (Price & Price, 2007).

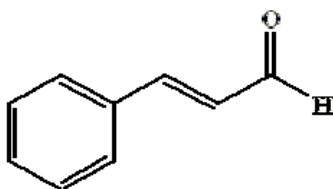


Figure 1: cinnamaldehyde

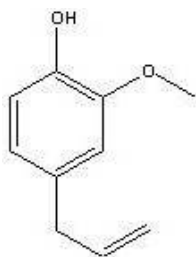


Figure 2: eugenol

- Herbal preparation(s)
  - a) Comminuted herbal substance
  - b) Liquid extract (DER 1:1) extraction solvent: 70% ethanol
  - c) Tincture (ratio of herbal substance to extraction solvent 1:5) extraction solvent: 70% ethanol
  - d) Essential oil obtained by steam distillation from the cortex
- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

See section 1.2 'Information about products on the market in the Member States'

– **Vitamins**

The drug contains per 100 g:

- vitamin A: 260 IU
- thiamine: 0.02 mg
- riboflavin: 0.14 mg
- niacin: 1.3 mg
- ascorbic acid: 28 mg

(Duke, 1988)

– **Minerals**

The drug contains per 100 g:

- Ca: 1.228 mg
- P: 61 mg
- Fe: 38 mg
- Mg: 56 mg
- Na: 26 mg
- K: 500 mg
- Zn: 2 mg

(Duke, 1988)

## 1.2. Information about products on the market in the Member States

### Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combined preparations authorised
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only in food supplement
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combined preparations authorised
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only combined preparations with cinnamon as a flavouring agent
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combined preparations authorised
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Germany	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only herbal tea and combined products with cortex and essential oil
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Essential oil and combined preparations authorised
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or

					registered preparations
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only combined preparations
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Food supplements with essential oil (5 drops 3x/d)
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combined products

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

## Specific information about preparations in the EU

### Austria

- several liquid extracts of the drug in combination products for gastrointestinal complaints or as a flavouring excipient

### Czech Republic

- solution for oral or external use containing extracts from *Melissae folium*, *Inulae radix*, *Angelicae radix*, *Zingiberis radix*, *Caryophylli flos*, *Galangae radix*, *Piperis nigri fructus*, *Gentianae radix*, *Myristicae semen*, *Aurantii pericarpium*, *Cinnamomi cortex*, *Cassiae flos*, *Cardamomi fructus*

### Germany

Cinnamon is one of the 13 ingredients of a solution for oral or external use (see above).

### Estonia

- the same combination preparation as mentioned above

### Lithuania

- the same combination preparation as mentioned above and *Cinnamomi aetheroleum* in a nother product

## Poland

- combined preparation containing *Melissae aetheroleum*, *Caryophylli aetheroleum*, *Cinnamoni aetheroleum*, *Citri limoni aetheroleum*, *Menthae piperitae aetheroleum*, *Lavandulae aetheroleum* and menthol in ethanol

### 1.3. Search and assessment methodology

#### Basic sources searched for *Cinnamomum verum* and *Cinnamomum zeylanicum*

- Barnes J, Anderson LA, Philipson JD. Herbal medicines. 3<sup>rd</sup> edition. Pharmaceutical press; 2007
- Bisset NG. *Cinnamomi cortex*. In: Herbal drugs and phytopharmaceuticals. Medpharm Scientific Publishers, Stuttgart; 1994
- Delfosse M. Drogues végétales plants médicinales. Service Scientifique de l'Association Pharmaceutique Belge; 1998
- Duke JA. *Cinnamomum verum*. In: Handbook of medicinal herbs. CRC Press; 1988
- E/S/C/O/P Monographs. The scientific foundation for herbal medicinal products. 2<sup>nd</sup> ed. Thieme, 2003
- European Pharmacopoeia 6.0. Cinnamon. 2009
- European Pharmacopoeia 6.2. Cinnamon bark oil, Ceylon. 2009
- Hänsel R, Keller K, Rimpler H, Schneider G. editors. *Cinnamomi cortex*. In: Hagers Handbuch der Pharmazeutischen Praxis. Berlin. Springer-Verlag; 1992
- Keller K, Hänsel R, Chandler RF. Adverse Effects of Herbal Drugs: *Cinnamomum* species. Volume 1 by P.A.G.M. De Smet. Springer Verlag, Heidelberg 1992
- Kommission E. *Cinnamoni ceylanici cortex*. Deutscher Apotheker Verlag; 1990
- Madaus: <http://www.henriettesherbal.com/eclectic/madaus/cinnamomum.html> 1938
- Price S, Price L. Aromatherapy for health professionals. 3<sup>rd</sup> edition. Churchill Livingstone Elsevier; 2007
- Todd G. Extra Pharmacopoeia Martindale. The Pharmaceutical Press, London 1967
- WHO monographs on selected medicinal plants. volume1. World health Organisation Geneva; 1999

#### EMA documents retrieved

CVMP Committee for Veterinary Medicinal Products. *Cinnamomi ceylanici cortex*. Summary report. The European Agency for the Evaluation of Medicinal Products. Evaluation of Medicines For Veterinary Use. EMEA/MRL/713/99-FINAL; Jan 2000, 1-3.

#### Search in databases:

- PubMed
- International Pharmaceutical Abstracts
- Biological abstracts

Keywords: *cinnamomum*, cinnamon, *cinnamomum verum* *cinnamomum zeylanicum* alone or combined with volatile oil, essential oil, cortex, bark.



## 2. Historical data on medicinal use

### 2.1. Information on period of medicinal use in the Community

- Historical use

Cinnamon has been used as a spice for thousands of years. In Egypt, cinnamon was a spice used in embalming fluids. In Ayurvedic medicine, cinnamon bark was used as an antiemetic, antidiarrheal, antifatulent and as a general stimulant. The Portuguese found cinnamon trees growing in Sri Lanka (Ceylon) in the early 16th century; they subsequently imported cinnamon to Europe during the 16th and 17th centuries. The Dutch occupied Sri Lanka in the mid-17th century until the British captured the island in 1796. The East India Company then became the main exporter of cinnamon to Europe. The Dutch cultivated cinnamon in Java and the exports of Ceylon cinnamon decreased as a result of heavy export duties. Nevertheless, Sri Lanka is the only regular supplier of cinnamon bark and leaf oils. The food industry prefers Ceylon cinnamon, but pharmaceutical manufacturers use both, oils from Ceylon cinnamon (cinnamon oil) and from Chinese cinnamon (cassia oil) interchangeably. China is the main exporter of cassia cinnamon (Barceloux, 2009).

Cinnamon belongs to the herbal substances with one of the longest medicinal traditions. It has been mentioned in the Bible, as well as by Greek and Roman literature (amongst others Theophrast, Herodot, Dioskurides, Galenus and Plinius). There is however no real reference to Ceylon as its original source. Dioskorides described 5 cassia and 7 cinnamon species. The latter ones were reported as possessing diuretic and digestive properties. From the 8<sup>th</sup> century, cinnamon was introduced in Europe as an expensive spice that only could be used by kings and popes. There is a written report on the use of cinnamon in an Arabian source from around 1275. In 1310, Johannes of Montevino confirmed the existence of cinnamon trees in Ceylon. About 100 years later, Nicolo Conit provided a real description of the cinnamon tree.

Introduced by the Portuguese, cinnamon of Ceylon remained the preferential substance in Europe. It has been described, that in 1536 cinnamon of Ceylon would have cost 40 times more than the cinnamon from Java or the Philippines. The herbal substance was first collected from wild growing trees. The cultivation of cinnamon started around 1765, when Holland took the lead in the source area. The production was streamlined in the way that a better quality was obtained and Holland could provide enough cinnamon to cover the European needs. When the English took over in 1796, the cinnamon cultivation and trading became a monopoly of the English Eastern-Indian Company. Around 1833, when Holland developed the cultivation of cinnamon in Java and Sumatra, the herb and the essential oil were introduced into medicine as a stimulant and cardiostimulant. The oil was prepared for the first time by St Amando of Doornyk at the end of the 15<sup>th</sup> century.

Cinnamon oil has been reported as an herbal medicine in case of nerve sensitivity. Higher doses were used to stimulate the cardiovascular system, nerves and muscles, more particularly the uterus. Higher doses could have an abortive effect and could lead to methaemoglobinaemia and nephritis. The oil should also have an antibacterial activity against typhus (Madaus, 1938).

- More recent and current use in the Community

See sections 1.2, 2.2 and 2.3

## **2.2. Information on traditional/current indications and specified substances/preparations**

When going back in history, cinnamon was used as stomachic and in case of nerve weakness. As the gastrointestinal use is concerned, cinnamon was used in case of diarrhoea, dyspepsia, hyperacidity with reflux, vomiting and bloating (Madaus, 1938).

Posologies suggested by Madaus (1938):

Herbal substance: 0.62 g-1.9 g

Tincture (without specification): 10-50 drops

Powder: 0.3-1.5 g several times daily

Maximal daily doses are not specified.

The herbal preparations are in traditional medicinal use for over 30 years (Wahrig & Richter, 2009).

### **The following indications have been reported for cinnamon:**

Dyspeptic complaints such as gastrointestinal spasms, bloating and flatulence, loss of appetite and diarrhoea (ESCOP, 2003; BHP, 1983; Bradley, 2006).

Cinnamon is used primarily as a taste enhancer and as a spice, and to some extent also in preparation of liquors.

Indications in folk medicine: diarrhoea, dyspeptic complaints, cold and flu, topical use for wound-cleaning. Except for diarrhoea and dyspeptic complaints, the indications in folk medicine have not been sufficiently documented (Hänsel *et al.*, 1992). The essential oil is used drop-wise ("cinnamondrops") as a remedy on dysmenorrhoea and to stop bleeding (Bisset, 1994).

Another source lists the following indications: application as an astringent, germicide, and antispasmodic. Cinnamon was one of the early treatments for chronic bronchitis, treatment of impotence, frigidity, dyspnea, inflammation of the eye, leukorrhoea, vaginitis, rheumatism, and neuralgia, as well as wounds and toothaches (Barceloux, 2009).

### **Indications for combination preparations:**

Czech Republic, Estonia and Lithuania:

- solution for oral use as an adjuvant at mild psychovegetative disturbances such as loss of appetite and gastrointestinal complaints, mood changes and headache of different origin, nervousity, restlessness, sleep disorders and as an adjuvant in common cold; externally used as mild remedy in neuritis, muscle pains, lumbago and gingivitis

## **2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications**

### **Posology and method of administration**

*Adolescents, adults:*

**dried bark:** 1.5-4 g daily; 0.5-1.0 g as an infusion three times daily (Barceloux, 2009; Hänsel *et al.*, 1992; Delfosse, 1998; ESCOP, 2003; WHO, 1999; Kommission E, 1990; Barnes *et al.*, 2007)

**fluid extract:** 0.5-1.0 ml (1:1) extraction solvent 70% ethanol V/V, three times daily (Hänsel *et al.*, 1992; ESCOP, 2003; Barnes *et al.*, 2007)

**tincture:** 2-4 ml daily (1:5) extraction solvent 70% ethanol V/V, to be given in 3 doses (Hänsel *et al.*, 1992; ESCOP, 2003; Barnes *et al.*, 2007; Todd, 1967)

**aetheroleum:** 50-200 mg daily, to be given in 3 doses (CVMP, 2000; Delfosse, 1998; WHO, 1999; Todd, 1967)

**spiritus:** (1 part of oil in 10 of ethanol 90%) 0.3 to 1.2 ml daily, to be given in 3 doses (Todd, 1967)

All preparations are orally administered.

*Elderly:* the same dose as for adults

### **Method of administration**

Oral use

If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted (Barnes *et al.*, 2007; ESCOP, 2003; Kommission E, 1990).

## **3. Non-Clinical Data**

### **3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

#### ***In vitro* tests**

##### Flatulence:

A foam generator was used as a model of flatulence for generating and assessing foams in digestive fluids *in vitro*. The effects of volatile oils, including cinnamon oil on gastric and intestinal foams were examined. Reductions in the foam volume were observed in every case, although the effects were not as high as those produced by a combination of dimethicone and silica. m-Cresol, p-hydroxybenzaldehyde, isobutanol, menthol and phenoxyethanol also reduced the foam volume, but the anti-foaming activity could not be related to published data on the ability to produce a 50% inhibition of a standard response in guinea pig ileum to carbachol. It suggested that carminative action is a combination of effects, one of which is a reduction of gastrointestinal foam (Harries *et al.*, 1978).

##### Spasmolytic activity:

Papaverine-like spasmolytic effects of cinnamon bark oil (EC<sub>50</sub> 41 mg/litre) and cinnamaldehyde were observed in tests on guinea pig tracheal and ileal smooth muscle. The results were compared with the relaxant effects of catecholamines and phosphodiesterase inhibitors. With regard to the relaxant effects, the examined oils, including cinnamon bark oil, were more potent on the ileal than on the tracheal muscle. However, a small group of oils had a higher relaxant effect on the tracheal than on the ileal muscle. This was also found to be the case with eugenol, eugenol acetate and cinnamic aldehyde (components of cinnamon oil) as well as with isoprenaline and phosphodiesterase inhibitors (Reiter *et al.*, 1985).

#### Antifungal activities:

The antifungal activities are mainly contributed to the essential oil (in concentrations ranging from 1% to 0.0025 %) and its active compound cinnamaldehyde inhibiting the growth of fungi and yeasts as well as their mycotoxin production: e.g. *Aspergillus clavus*, *A. niger*, *A. parasiticus*, *Candida albicans* (Kalemba & Kunicka, 2003). Cinnamon bark oil also inhibits the growth of several dermatophytes. The inhibitory zone induced by cinnamon bark oil in solid media was 28 mm in diameter, comparable to the 20-25 mm zone induced by ketoconazole at 100 µg/ml (Lima *et al.*, 1993). The essential oils' most active constituents upon mycelial growth were also the most active against aflatoxinogenesis. However, the examined essential oils inhibited the aflatoxin synthesis to a higher extent than the mycelial growth (Tantaoui-Elaraki & Beraoud, 1994).

#### Antibacterial properties:

The essential oil was screened against four gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*) and two gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) at four different concentrations (1:1, 1:5, 1:10 and 1:20) using the disc diffusion method. The minimum inhibitory concentration (MIC) of the active essential oils was tested using two fold agar dilution method at concentrations ranging from 0.2 to 25.6 mg/ml. A zone of inhibition above 7 mm in diameter was taken as positive result. Cinnamon oil exhibited a promising inhibitory effect, showing inhibitory activity, even at low concentration, on both gram-positive and gram-negative bacteria. Cinnamon oil showed inhibitory effect against *P. aeruginosa* (33.3 mm), *B. subtilis* (29.9 mm), *P. vulgaris* (29.4 mm), *K. pneumoniae* (27.5 mm) and *S. aureus* (20.8 mm) (Prabuseenivasan *et al.*, 2006).

The antimicrobial activity against the food-borne pathogenic gram positive bacteria of *Listeria monocytogenes* Scott A were studied in semi-skimmed milk incubated at 7°C for 14 days and at 35°C for 24 h. The MIC for cinnamon bark essential oil was 500 ppm. The effective concentration increased to 1,000 ppm when the semi-skimmed milk was incubated at 35°C for 24 h and the Minimum Bactericidal Concentration (MBC) was rated 3,000 ppm. The influence of the fat content of milk on the antimicrobial activity of the essential oil was tested in whole and skimmed milk. In milk samples with higher fat content, the antimicrobial activity of the essential oil was reduced. These results indicate the possibility of using essential oil of cinnamon in milk beverages as a natural antimicrobial (Cava *et al.*, 2007).

#### Anti-inflammatory activity:

Various essential oils, including cinnamon bark oil, used in the treatment of rheumatism and inflammation as well as some of their main constituents and phenolic compounds known for their irritant and pungent properties were screened for activity as inhibitors of prostaglandin biosynthesis. A combination of a prostaglandin-synthesizing cyclo-oxygenase system from sheep seminal vesicles and an HPLC separation technique for the metabolites of arachidonic acid was used as test system. Cinnamon bark oil showed inhibitory cyclo-oxygenase activity. The active compound is probably eugenol (Wagner *et al.*, 1986).

#### Effects on human spermatozoa:

The effect of cinnamon oil on human spermatozoa *in vitro* was studied. Fresh ejaculates were obtained from male partners of infertile couples. Cinnamon bark oil showed a spermicidal effect with a minimum concentration of 1:400 V/V. The percentage change in motility over control was calculated. The spermicidal action was confirmed by a supra-vital staining. Higher dilutions of the volatile oil were also spermicidal when incubated with semen samples for a longer period (Buch *et al.*, 1988).

### Cytotoxicity:

Petroleum ether (25:1) and chloroform (68:1) extracts of cinnamon exhibited cytotoxic effects with respective ED<sub>50</sub> values of 60 and 58 µg/ml in human cancer (KB) cells and 24 and 20 µg/ml in mouse leukemia L1210 cells (Chulasiri *et al.*, 1984).

Cinnamaldehyde, also cytotoxic to rat hepatocytes, is the reactive cinnamyl species, since this compound is the most potent intracellular glutathione (GSH) depletor and exhibits the highest cytotoxicity in hepatocyte suspensions with a threshold cytotoxic concentration of 10<sup>-3</sup> M. Predepletion of GSH with diethyl maleate and/or inhibition of γ-glutamylcysteine synthetase by l-buthionine S,R-sulfoximine reduces the threshold concentration for cytotoxicity. Intracellular GSH was progressively depleted by cinnamaldehyde in a concentration-dependent manner from 10<sup>-4</sup> to 10<sup>-3</sup> M (Swales & Caldwell, 1996).

### Antiproliferative activity

Trans-cinnamaldehyde (CA) and its analogues 2-hydroxycinnamaldehyde and 2-benzoyloxycinnamaldehyde have been reported to possess antitumor activity. CA is also a known activator of the transcription factor Nrf2. Cinnamaldehyde analogues were synthesized and screened for antiproliferative and thioredoxin reductase (TrxR)-inhibitory activities. Whereas CA was weakly cytotoxic and TrxR inhibiting, hydroxy and benzoyloxy substitutions resulted in analogy with enhanced antiproliferative activity paralleling increased potency in TrxR inactivation. TrxR inactivation contributes at least partly to cinnamaldehyde cytotoxicity. These Michael acceptor molecules can potentially be exploited for use in different concentrations in chemotherapeutic and chemo-preventive strategies (Chew *et al.*, 2009).

### ***In vivo* tests**

#### Spasmolytic and cardiovascular activity:

Effects of cinnamaldehyde on the cardiovascular and digestive systems were examined. A papaverine-like muscolotropic activity of cinnamaldehyde seemed to be involved in the vasodilatation.

Cinnamaldehyde, administered intravenously at 5 and 10 mg/kg body weight, moderately inhibited both the rat stomach movement and the mouse intestinal propulsion and had a stimulating effect on the cardiovascular system. Concentrations of 10<sup>-4</sup>–10<sup>-5</sup> g/ml were used in organ preparations. Gastric erosions produced in stressed mice were protected by oral administration of cinnamaldehyde. When administered intravenously to dogs at 5 and 10 mg/kg body weight, cinnamaldehyde had a dose-dependent hypotensive effect (Harada & Jano, 1975).

Other studies have shown that cinnamaldehyde is an inhibitor of stomach peristalsis in anaesthetised rats (5-20 mg/kg intravenously) and of the peristalsis in the gut of mice (250 mg/kg intraperitoneally). Cinnamaldehyde also stimulates bile secretion in rats (500 mg/kg), has central nervous system stimulating activity in rabbits (10-20 mg/kg intra-arterially) and inhibits motor activity in mice (250-1000 mg/kg oral doses) (CVMP, 2000).

#### Anti-nociceptive activity:

Dry ethanolic extract of *Cinnamomum zeylanicum* administered orally to mice at 200 and 400 mg/kg body weight exhibited analgesic effects on the hot plate thermal stimulation and the acetic acid induced writhing tests in a dose dependent manner (Atta & Alkofahi, 1998).

#### Anti-inflammatory activity:

Dry ethanolic extract of *Cinnamomum zeylanicum* administered orally to rats at 400 mg/kg body weight showed an anti-inflammatory effect against chronic inflammation induced by cotton pellet granuloma indicating an anti-proliferative effect (Atta & Alkofahi, 1998).

### **3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

#### Metabolism

After application of cinnamaldehyde to rats, benzoic acid and cinnamic acid were found in urine samples (Hänsel *et al.*, 1992).

The pharmacokinetics of cinnamic acid (CA) after oral administration of a decoction of Ramulus Cinnamomi (RC) 7.4 g/kg [containing CA  $7.62 \times 10^{-5}$  mol/kg and cinnamaldehyde (CNMA)  $1.77 \times 10^{-5}$  mol/kg], was compared with that after oral administration of pure CA  $7.62 \times 10^{-5}$  mol/kg in rats. Plasma concentrations of CA and hippuric acid (HA) were determined by HPLC. Pharmacokinetic parameters were calculated from the plasma concentration-time data. CA was quickly absorbed and then metabolized mainly into HA. The AUC (0-t) and AUC (0- $\infty$ ) of CA were higher in RC group than those in pure CA group and the bioavailability of CA from RC was higher than that from pure CA. After intragastric administration of  $3.79 \times 10^{-4}$  mol/kg, CNMA was at least partially metabolized into CA in stomach and small intestine and almost completely metabolized into CA in liver before it is absorbed into blood in rats. The results showed that plasma CA in RC group might partly come from transformation of CNMA in RC (Chen *et al.*, 2009).

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

#### Acute toxicity:

The oral LD<sub>50</sub> of cinnamon bark oil in rats has been determined as 4.16 g/kg and 3.4 ml/kg body weight. For cinnamaldehyde the oral LD 50 in rats is 2.22 g/kg body weight. The dermal LD<sub>50</sub> of cinnamon bark oil in rabbits has been reported as 0.69 ml/kg and 0.59 mg/kg for cinnamaldehyde. The undiluted oil was severely irritating to the intact skin of rabbits and mildly irritating when applied to the backs of hairless mice; however, when tested at 8% in petrolatum it produced no irritation in 25 human subjects (ESCAP, 2003).

#### Sub-acute and chronic toxicity:

The acceptable daily intake of cinnamaldehyde was set to 700 µg/kg of body weight by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It was not extended because of inadequate toxicity data. The ADI of eugenol is up to 2.5 mg/kg (CVMP, 2000). Cinnamaldehyde added to the diet of sprague dawley rats for 16 weeks at 10 g/kg resulted in slight swelling of hepatic cells and slight hyperkeratosis of the squamous portion of the stomach; the no-effect level was at 1000 and 2500 mg/kg (ESCAP, 2003).

In 90-day studies on mice given an oral dose of 100 mg/day/kg of an ethanolic extract *C. zeylanici* cortex (*C. verum*, crude drug/extract ratio not given) report inducing an increase in reproductive organ weights, sperm motility, sperm count. The study failed to illicit any spermatotoxic effect reported in earlier *in vitro* studies (CVMP, 2000).

### Mutagenicity and genotoxicity:

Cinnamon extracts, cinnamon bark oil and cinnamaldehyde showed no mutagenic potential in several studies using the Ames test. The Ames *Salmonella* reversion assay was negative for cinnamaldehyde (Sekizawa & Shibamoto, 1982). Trans-cinnamaldehyde and trans-cinnamic acid were not mutagenic in five strains of *Salmonella typhimurium*. The mutagenicity tests were performed both without and with activation by rat and hamster liver microsomal preparations (Lijinsky & Andrews, 1980).

On the other hand, other studies, also using the Ames test, have shown mutagenic activity of cinnamon compounds. Cinnamon bark oil and cinnamaldehyde gave positive results in chromosomal aberration tests using Chinese hamster cell cultures as substrate (Ishidate *et al.*, 1984). Positive results in the Ames test were also obtained for alcoholic extracts of cinnamon (Keller *et al.*, 1992).

Cinnamaldehyde and cinnamyl alcohol were positive in the *Bacillus subtilis* DNA-repair test. Both compounds were negative in the *Escherichia coli* WP2 uvrA reversion test (Sekizawa & Shibamoto, 1982; Keller *et al.*, 1992).

In the *Bacillus subtilis* DNA repair test (repair-recombinant proficient strains), using *Bacillus subtilis* strains H17 (rec+) and M45 (rec-), the petroleum ether and the chloroform extracts of *C. verum* showed mutagenicity. On the contrary, the ethanol extract showed no mutagenic activity (Ungsurungsie *et al.*, 1984; Ungsurungsie *et al.*, 1982).

Cinnamon oil and cinnamaldehyde gave positive results in the chromosomal aberration tests using Chinese hamster cell cultures (Keller *et al.*, 1992). Cinnamaldehyde showed genotoxic effects in *Drosophila* test systems. In another study an aqueous extract of cinnamon gave a negative result in a similar *Drosophila* test system (ESCOP, 2003; Keller *et al.*, 1992).

The results of the *in vitro* bacterial mutagenicity tests must be interpreted with caution because the concentrations used were within the dose range where antimicrobial effects of cinnamaldehyde and cinnamon oil have been proven. Furthermore, growth retardation due to antimicrobial effect is the reason for the reported 'antimutagenic' effect of cinnamaldehyde (Keller *et al.*, 1992).

Concentrations of 50, 100, 200, 300, 500, 1000 and 2000 µ/ml of the essential oil of *Cinnamomum verum* were tested in *Salmonella typhimurium* strains TA100 with and without rat liver S9 using the Ames *Salmonella* reversion assay. Results: without S9 fraction, increase in mutant colonies per plate was not observed with any of the used concentrations. Also with the S9 fraction none of the samples caused a significant increase in mutant colonies per plate (Shoeibi *et al.*, 2009).

### Carcinogenicity:

According to Keller *et al.* (1992) unspecific cytotoxic effects *in vitro* are strongly influenced by the culture medium and other experimental conditions. On the other hand, cinnamaldehyde inhibits thioredoxin reductase and can be considered as a candidate for cancer therapy and chemoprevention (see earlier Chew *et al.*, 2009).

### Teratogenicity:

Cinnamaldehyde was reported to exhibit teratogenic effects in chick embryos. The teratogenic dose was closely related to the toxic dose of cinnamaldehyde (0.5 mmol/embryo) with 58.2% malformations and 49 % lethality. However, a methanol extract of cinnamon given by gastric intubation was not teratogenic in rats (ESCOP, 2003).



### 3.4. Overall conclusions on non-clinical data

#### Pharmacology

The *in vitro* and *in vivo* tests on the spasmolytic activity of cinnamon bark oil and cinnamaldehyde show clear relaxant effect on the tracheal and ileal smooth muscles. The musculo-tropic activity of cinnamaldehyde also participates in vasodilatation. Anti-foaming activity may contribute to the carminative effect.

The essential oil has antimicrobial activity. It can inhibit the growth of fungi and yeasts like *Aspergillus* and *Candida*, including their mycotoxin production. Also the inhibition of dermatophytes has been observed. Inhibitory activity against aflatoxinogenesis is more pronounced than the inhibition of mycelial growth. Cinnamon oil also exhibited inhibitory activity towards both gram-positive and gram-negative bacteria *in vitro*. As for the cytotoxic effects, studies have been performed on mouse leukemia cells, rat hepatocytes and human spermatozoa and all studies have proven a certain degree of cytotoxicity.

The *in vivo* experiments on anti-inflammatory and anti-nociceptive activity of the ethanolic extracts of cinnamon showed positive results.

In general, the pharmacological effects and the antimicrobial activity described are obtained with high concentrations of cinnamon oil. They partially support the traditional indication but they cannot support a well-established use.

#### Pharmacokinetics

*In vivo* data on pharmacokinetics are available on cinnamic acid in cinnamon bark decoction as compared to pure cinnamic acid (Chen *et al.*, 2009). The oral bioavailability of cinnamic acid was higher when administered as the decoction. Cinnamaldehyde seems to be highly susceptible to oxidation. Pharmacokinetic data on the essential oil are absent.

#### Toxicology

Cinnamon oil contains cinnamaldehyde which is an irritating and sensitizing component that could be the cause of dermatitis. Most of the available data are related to cinnamaldehyde. When using the essential oil or extracts of cinnamon, the results are mostly negative. This makes data on mutagenicity of cinnamon rather contradictory and further investigation as to the beneficial role of the natural matrix is required. Investigations on mutagenicity and genotoxicity are insufficient to fully evaluate the carcinogenic risk of cinnamon. The data on teratogenicity are considered to be of limited value for the risk assessment for use by humans (WHO Monographs, 1999).

In summary, the data on toxicity are insufficient. Therefore a list entry cannot be recommended.

## 4. Clinical Data

### 4.1. Clinical Pharmacology

#### 4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

A small scale clinical study by Khan *et al.* (2003) included 60 patients with type 2 diabetes, randomly divided into groups. As medication capsules contained *Cinnamomum cassia* 1.3 or 6 g daily (part of the plant not specified). The capsules were given as an add-on therapy to antidiabetic medication. The cinnamon was consumed 40 days followed by a 20-day washout period. The effects on the blood



glucose, triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels were measured. After 40 days, all the three levels of cinnamon reduced the mean fasting serum glucose (18-29%), triglyceride (23-30%), LDL cholesterol (7-27%), and total cholesterol (12-26%) levels while no significant changes were noted in the placebo groups. The changes in HDL cholesterol were not significant.

An aqueous purified extract of *Cinnamomum cassia* (plant part not specified) was administered to 79 diabetes mellitus type 2 patients three times daily for 4 months. The amount of aqueous cinnamon extract corresponded to 3 g of cinnamon powder daily. There was a higher reduction of fasting plasma glucose level (10.3%) in the cinnamon group than in the placebo group (3.4%). No significant differences were observed regarding glycated haemoglobin (HbA<sub>1c</sub>), lipid profiles or differences between the pre- and post-intervention levels of these variables. The decrease in plasma glucose correlated significantly with the baseline concentrations, indicating that subjects with a higher initial plasma glucose level may benefit more from cinnamon intake (Mang *et al.*, 2006).

The influence of *Cinnamomum cassia* on glucose homeostasis was investigated in 7 lean healthy volunteers (26 ± 1 years; BMI 24.5 ± 0.3). They underwent an oral glucose tolerance test (OGTT) supplemented with either placebo or 5 g powdered *Cinnamomum cassia* (most probably bark powder). The cinnamon ingestion reduced total plasma glucose response (AUC) to 75 g glucose orally ingested. When ingested with the glucose, cinnamon reduced the plasma response to glucose with 13%; when ingested 12 hours prior to glucose, this reduction was 10% (both p<0.05). This study proves an immediate and long lasting (12 hours) effect of *Cinnamomum cassia* on glucose in plasma (Solomon & Blannin, 2007).

Eight male volunteers (aged 25 ± 1 years, body mass 76.5 ± 3.0 kg, BMI 24.0 ± 0.7 kg/m<sup>2</sup>; mean ± SEM) underwent two 14-day interventions involving cinnamon (6 capsules each containing 500 mg *Cinnamomum cassia*, part of the plant not specified) or placebo supplementation. Placebo supplementation was continued for 5 days following this 14 day period. Oral glucose tolerance tests (OGTT) were performed on days 0, 1, 14, 16, 18, and 20. The cinnamon ingestion reduced the glucose response to OGTT on day 1 (-13.1 ± 6.3% vs. day 0; P = 0.05) and day 14 (-5.5 ± 8.1% vs. day 0; P = 0.09). The cinnamon ingestion also reduced insulin responses to OGTT on day 14 (-27.1 ± 6.2% vs. day 0; P = 0.05), as well as improving insulin sensitivity on day 14 (vs. day 0; P = 0.05). These effects were lost following cessation of cinnamon feeding. *Cinnamomum cassia* may improve glycaemic control and insulin sensitivity, but the effects are quickly reversed (Solomon & Blannin, 2009).

A limited number of subjects (N = 22) with impaired fasting blood glucose and a BMI ranging from 25 to 45 were enrolled in a double-blind placebo-controlled trial. Subjects were given capsules containing either placebo or 250 mg of a dried aqueous extract of *Cinnamomum cassia* (Cinnulin PF, part of the plant not specified) two times daily for 12 weeks.

Plasma malondialdehyde (MDA) concentrations were assessed using high performance liquid chromatography and plasma antioxidant status was evaluated using ferric reducing antioxidant power (FRAP) assay. Erythrocyte Cu-Zn superoxide (Cu-Zn SOD) activity was measured after hemoglobin precipitation by monitoring the auto-oxidation of pyrogallol and erythrocyte glutathione peroxidase (GPx) activity by established methods.

FRAP and plasma thiol (SH) groups increased, while plasma MDA levels decreased in subjects receiving the cinnamon extract. The effects were more pronounced after 12 than 6 weeks. There was also a positive correlation (r = 0.74; p = 0.014) between MDA and plasma glucose. This study supports the hypothesis that the inclusion of water soluble compounds of *Cinnamomum cassia* reduces risk factors associated with diabetes and cardiovascular disease (Roussel *et al.*, 2009).

Rudowska (2009) made an overview of studies done with *Cinnamomum cassia* to influence blood glucose. They consider the herbal preparation as a functional food. According to the author, fasting

blood glucose seems to be reduced by cinnamon supplements in men and women with the metabolic syndrome. Also a high dose (6 g/d) of cinnamon with a rice pudding reduces postprandial blood glucose and delays gastric emptying without affecting satiety. However, other studies could not replicate these findings. Cinnamon supplementation (1.5 g/d) did not improve whole-body insulin sensitivity, oral glucose tolerance or blood lipid profile in postmenopausal patients with type 2 diabetes. Prospective randomized controlled trials indicate that the use of cinnamon does not confirm to improve Fasting Blood Glucose (FBG), glycosylated hemoglobin (HbA1c) or lipid parameters in patients with type 1 or type 2 diabetes.

#### **4.1.1.1. Overall conclusions on pharmacodynamics**

Clinical pharmacological data of *Cinnamomum verum* preparations do not exist. The plausibility of the efficacy is based on the traditional medicinal use and supported by the non-clinical data.

Recent studies with a different *Cinnamomum* species, *C. cassia*, showed a hypoglycemic effect (Khan *et al.*, 2003; Mang *et al.*, 2006). The studies are not related to *C. verum*.

General data on the base of other plant species cannot be considered. From the traditional use of *C. verum* no clinical hypoglycaemic effects are reported.

#### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available.

##### **4.1.2.1. Overall conclusions on pharmacokinetics**

Clinical data on absorption, distribution and pharmacokinetic interactions are not available.

### **4.2. Clinical Efficacy**

#### **4.2.1. Dose response studies**

Not data available.

#### **4.2.2. Clinical studies (case studies and clinical trials)**

Data only available for *Cinnamomum cassia* (see 4.1.1).

#### **4.2.3. Clinical studies in special populations (e.g. elderly and children)**

Not data available.

### **4.3. Overall conclusions on clinical pharmacology and efficacy**

Currently there's no data available on clinical efficacy.

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

No data available.

## 5.2. Patient exposure

No data available.

## 5.3. Adverse events and serious adverse events and deaths

### Cinnamon bark oil

Undiluted cinnamon bark oil was mildly irritating when applied to the backs of hairless mice and strongly irritating under occlusion to both intact and abraded rabbit skin.

The preparation of 8% in petrolatum did not cause irritation but gave sensitization reactions in humans. Also cases of contact sensitivity to a dentifrice containing the oil have been reported.

It is recommendable to avoid the use of the oil per os in liver conditions, alcoholism and when taking paracetamol because of the glutathione depleting action of cinnamaldehyde (Price & Price, 2007).

Cinnamaldehyde, one of the components of the essential oil, 5% in petrolatum is a skin irritant.

Cinnamon oil caused second-degree burns of after 48 hours of contact on the skin of an 11-year-old boy (Keller *et al.*, 1992).

Extensive reporting on side effects of cinnamon is done by Barceloux (2009). Most case reports of toxicity from the cinnamon oil involve local irritation and allergic reactions to the cinnamon oil as a constituent of a personal hygiene (toilet soaps, mouthwash, toothpaste, perfumes, mud baths), beverages (colas, vermouth, bitters), or baking products. Allergic reactions include contact dermatitis, perioral dermatitis, cheilitis, stomatitis, gingivitis, glossitis, chronic lichenoid mucositis, contact urticaria, 24 and rarely immediate hypersensitivity reactions (asthma, urticaria). Clinical manifestations of intraoral reactions include pain, swelling, erythema, ulcerations, fissures, vesicles, and white patches. These reactions are local, and distal skin involvement is rare. Occupational allergic contact dermatitis from spices is rare, and typically involves the hands. More common food sensitizers include carrot, cucumber, tomato, melon, fish, potato, orange, green pepper, onion, red cherry, and garlic. Cinnamon oil contains local mucous membrane irritants such as cinnamaldehyde and cinnamic acid.

Prolonged skin contact (48 hours) from a cinnamon oil spill produced superficial partial-thickness burns. Chronic use of a cinnamon flavored gum can produce sub-mucosal inflammation and alteration of the surface epidermis resembling oral leukoplakia, manifest on biopsy by acanthosis, hyperkeratosis, parakeratosis, plasma cell infiltration, fibrosis of the lamina, and focal atypia. These changes are not pathognomonic for cinnamon-induced mucositis. The differential diagnosis of chronic mucositis associated with hypersensitivity to cinnamon includes local trauma, smokeless tobacco keratosis (snuff dipper's lesion), hyperkeratosis, lichen planus, lupus erythematosus, candidiasis, premalignant lesions, lichenoid mucositis, and carcinoma.

The severity of the local mucosal reaction depends on the duration of cinnamon-gum chewing. In contrast to the diffuse gingival reaction associated with cinnamon-flavored toothpaste, oral lesions associated with gum chewing occur on the lateral border of the free tongue or adjacent buccal mucosa. Sequelae of contact dermatitis associated with cinnamon include desquamation and hyperpigmentation. Although a case report associated the development of squamous cell carcinoma of the tongue with prolonged use of cinnamon gum, the International Agency for Research on Cancer (IARC) and the US National Toxicology Program do not list cinnamon as a potential carcinogen. School-aged children abuse cinnamon oil by sucking on toothpicks or fingers dipped in the oil. Reported effects include facial flushing, sensation of warmth, and intraoral hyperesthesias. Although nausea and abdominal pain may occur, systemic symptoms do not usually result from this type of exposure. Ingestion of cinnamon oil may cause central nervous system depression, predisposing the patient to aspiration pneumonia (Barceloux, 2009).

### **5.3.1. Serious adverse events and deaths**

Severe reactions such as anaphylaxis have not been reported. All cases with side effects recovered when the cinnamon containing preparation was withdrawn. Nevertheless, preparations with more than 0.01% cinnamaldehyde are suspect according to Keller *et al.* (1992).

### **5.4. Laboratory findings**

No data available.

### **5.5. Safety in special populations and situations**

Patients with an allergy to cinnamon or Peru balsam are contra medicated (WHO monographs, 1999). Cinnamon bark oil must be regarded as a potential sensitizer on the skin. It should not be used on young children and elderly people. Because of the experimentally demonstrated glutathione depleting activity of cinnamaldehyde, it is recommendable to avoid administering cinnamon bark oil *per os* to patients suffering from liver conditions, in case of alcoholism and when taking paracetamol (Price & Price, 2007).

### **5.6. Intrinsic (including elderly and children) /extrinsic factors**

No special studies about the use in children or elderly exist.

### **5.7. Drug interactions**

No drug interactions are mentioned for *Cinnamomum zeylanicum*.

*Cinnamomum cassia* bark (2 g in 100 ml) markedly retarded the *in vitro* dissolution of tetracycline. HCl from gelatine capsules: only 20% dissolved within 30 minutes in contrast to 97% when only water was used. The effect was attributed to the adsorption of the antibiotic on the particles. There are no further investigations to establish which individual constituents of cassia bark (volatile oil, cinnamaldehyde or mucilage) are responsible for this effect. As a dose of 1 to 2 g cinnamon is not uncommon, it is recommended not to use tetracyclines together with cinnamon at that dose level (Keller *et al.*, 1992).

### **5.8. Use in pregnancy and lactation**

Only limited data are available. The data are not sufficient for an adequate benefit/risk assessment. In accordance with general medicinal practice, Cinnamomi cortex products should not be used during pregnancy and lactation (WHO monographs, 1999).

Cinnamon was used in antiquity and the middle ages as abortifacient. It must be taken into account that in old sources cinnamon (cassia) was confused with *Cassia fistulosa* which contains anthraquinone (Keller *et al.*, 1992).

An unspecified 'large amount of cinnamon' was reported to have caused methemoglobinemia, hematuria, albuminuria and cylindruria in pregnant women. Abortion was not reported. The daily intake of 100 drops of a non specified tincture of cinnamon did not result in abortion (Keller *et al.*, 1992).

### **5.9. Overdose**

Cinnamon bark oil and cinnamaldehyde in doses over 0.2 g/day (equivalent to 15-20 g of crude drug) have irritant properties (ESCOP, 2003).

A case report of massive ingestion of 60 ml cinnammon oil has been published. The patient, a 7.5-year-old child, immediately felt a burning sensation in the throat and stomach, experienced a double vision and had a warm dry skin. The child exhibited sleepiness, dizziness and a rapid pulse (100 beats/min) (Pilapil, 1989).

### **5.10. Drug abuse**

Cases of cinnamon oil abuse were documented in adolescents and children. Sucking on toothpicks or fingers which had been dipped in cinnamon oil was the primary method of abuse. The subjects experienced a rush or sensation of warmth, facial flushing, and oral burning. Some children complained of nausea or abdominal pain but no systemic effects were reported (Perry *et al.*, 1990).

### **5.11. Withdrawal and rebound**

None known.

### **5.12. Effects on ability to drive or operate machinery or impairment of mental ability**

None known.

### **5.13. Overall conclusions on clinical safety**

The efficacy of *Cinnamomum verum* is plausible on the basis of long standing use and experience. The traditional use over a long period has shown that *C. verum* is not harmful when used in the specified conditions. However, a long standing excessive use does not exclude concerns with regard to the product safety. Therefore *C. verum* should not be used during pregnancy and lactation, in cases of fever of unknown origin, stomach or duodenal ulcers, and in patients with an allergy to cinnamon or Peru balsam. No drug interactions are documented. There is no restriction to the duration of use of the herbal substance.

## **6. Overall conclusions**

Despite of their long tradition, the bark and the essential oil of *Cinnamomum verum* do not fulfil the requirements of a well-established medicinal use with recognised efficacy. Cinnamon products may be considered as traditional herbal medicinal products on the basis of the long medicinal tradition in the specified conditions.

### **Benefit-risk assessment**

- Quality

The herbal substance or the dried bark of *Cinnamomum verum* is described in the European Pharmacopoeia. Quality relates to its content of essential oil. There are no cases of contamination or adulteration mentioned in the literature. The odour of the herbal substance can be considered as an important tool in the identification process.

Conclusion: analytical assessment of the quality of *Cinnamomum* should be made and the shelf-life of the preparations should be monitored.

- Safety

Cinnamon has been used in Europe since the 13<sup>th</sup> century. Patients with liver pathology should avoid taking cinnamon because there may be a glutathione depleting action of cinnamaldehyde. No serious adverse effects have been reported. Ingestion of supratherapeutic amounts of cinnamon oil (equivalent to 15 to 20 g bark) can lead to gastro-intestinal irritation and even to central effects like sleepiness, dizziness and a rapid pulse. It should be taken into consideration that all preparations included in the regulatory overview were complex mixtures of which cinnamon oil was one of the components. Administered in such way, does make gastro-intestinal irritation less probable.

Abuse of the cinnamon oil has been described. Most of the cases reported up to now are not in a medico-pharmaceutical context. Therefore a warning should not be included in the monograph. There is only limited preclinical information with regard to the pregnancy and lactation. High doses were teratogenic for chicken embryos.

Cinnamaldehyde and other cinnamon compounds were mutagenic in the Ames test and the chromosome aberration test. Cinnamaldehyde was genotoxic in the *Drosophila* test system. Tests with the isolated compounds, however, are of limited value for the possible risks with the herbal substance.

Conclusion: there is no major concern about the safety of *Cinnamomum verum* bark preparations under conditions given in the monograph.

Cinnamon bark and essential oil were not adequately tested on genotoxicity where positive effects were obtained for isolated compounds. Therefore a list entry can not be considered.

- Efficacy

Cinnamon has been used for centuries for dyspeptic complaints. It has to be considered for symptomatic treatment after serious illness is excluded.

Conclusion: see safety conclusion.

## **Annex**

### ***List of references***