24 November 2014
EMA/HMPC/715093/2013
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Carum carvi* L., fructus and *Carum carvi* L. aetheroleum

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Carum carvi* L., fructus
Herbal preparation(s)	Carvi fructus a) Comminuted herbal substance Carvi aetheroleum a) Essential oil obtained by steam distillation from the dry fruits of *Carum carvi* L.
Pharmaceutical forms	Carvi fructus a) Herbal substance or comminuted herbal substance as herbal tea for oral use. Carvi aetheroleum a) Herbal preparation in liquid dosage form for oral use. b) Herbal preparation in semi-solid dosage form for cutaneous use.
Rapporteur	Per Claeson
Assessor	Erika Svedlund
Peer-reviewer	Marisa Delbò

Note: This draft assessment report is published to support the release for public consultation of the draft European Uinon monograph on *Serenoa repens*, *fructus*. It should be noted that this document is a working document, not yet edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this draft assessment report. The publication of this draft has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

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

- Herbal substance

Caraway fruit is the whole, dry mericarp of *Carum carvi* L. and should contain a minimum 30 ml/kg of essential oil (anhydrous drug) in accordance with the European Pharmacopeia (01/2008:1080).

Carum carvi L. is included in the plant family Apiaceae (nom. alt. Umbelliferae) (The International Plant Names Index, 2014).

- Herbal preparations

Comminuted herbal substance.

Caraway oil is obtained by steam distillation from the dry fruits of *Carum carvi* L. in accordance with the European Pharmacopeia (01/2008:1817).

- Constituents

Caraway fruit

Caraway fruit contains 3-7 % v/m of essential oil, consisting largely of d-carvone (50-65 %), and (+)-limonene (up to 45 %), with less than 1.5 % of carveol and dihydrocarveol. It also contains 10-18 % of fixed oil, of which the main components are petroselinic (30-43 %), linoleic (34-37 %), oleic (15-25 %) and palmitic (4-5 %) acids. Other constituents include about 20 % of protein, about 15 % carbohydrates, phenolic acids, mainly caffeic acid, and traces of flavonoids such as quercetin, kaempferol and their glycosides. Carvenone, carvacrol and perillalcohol are found as distillation and storage artefacts (ESCOP, 2003).

Caraway oil

According to the European Pharmacopeia, caraway oil should contain 0.1-1 % β-myrcene, 30-45 % limonene, 50-65 % carvone and a maximum of 2.5 % of trans-dihydrocarvone and trans-carveol, respectively (Ph. Eur. 01/2008:1817).

d-Carvone

Carvone (p-mentha-6,8-dien-2-one) is a monoterpene ketone representative of the terpenes. The enantiomer d-carvone is a constituent of caraway and dill, whereas l-carvone is a constituent of spearmint oil. The racemate occurs in gingergrass oil (de Sousa *et al.*, 2007).

Synonyms for d-carvone: (+)-carvone; d(+)carvone; (S)-carvone; (S)-(+1-carvone; (S)-2-methyl-5-(l-methylethenyl)-2-cyclohexen-1-one; (S)-d-p-mentha-6-8,(9)-dien-2-one; (SI-(+)-p-mentha-6,8-dien-2-one; d-l-methyl-4-isopropenyl-6-cyclohexen-2-one (NTP, 1990).

- 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.

Not applicable.

1.2. Search and assessment methodology

Traditional medicinal use of caraway fruit and caraway oil has been documented in several handbooks that are included in the list of references. PubMed and TOXNET were searched in January 2014 using the terms [carum carvi], [caraway] and [carvone]. Also, the Mesh term [carum] was used. The abstracts of the references retrieved were screened manually and all articles considered relevant were assessed and included in the list of references.

The EudraVigilance database and Vigisearch database of the World Health Organization's were searched in February 2014 using the term [carum carvi].

Data was also provided by the EMA on behalf of interested parties.

Additionally, the European Commission´s databases on cosmetic ingredients (CosIng) was searched in April 2014 for information on [carum carvi], [caraway] and [carvone].

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products.

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Carum carvi L., fructus	Adjunctively as a carminativum in digestive disorders such as flatulence and indigestion.	Herbal tea for oral use. Adults and adolescents: 2 g in 150 ml of boiling water 1-3 times daily.	Before 1998 Poland
Carum carvi L., fructus	For digestive complaints with mild cramps in the gastro-intestinal area, bloating, flatulence	Herbal tea for oral use. Adults and adolescents 1.8 g crushed in 150 ml of boiling water 1-3 times daily	Since 1976 Germany
Carum carvi L., aetheroleum 10 g (=11.5 ml) ointment contains: 0.2 g caraway oil	To support digestive function and for relief of flatulence.	Ointment. Cutaneous use after bathing and in the evening. To be applied once daily as a thin layer on	Since 1976 Germany

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		the abdominal area.	

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

Caraway is one of the earliest cultivated herbs in Asia, Africa and Europe. Medicinal use of caraway fruit has been widespread in several ethnomedical systems from Northern Europe to the Mediterranean regions, Russia, Iran, India, Indonesia and North America (Johri, 2011).

In several medicinal European handbooks, the dried ripe fruits and essential oil of caraway is described as carminative (Madaus, 1938, Ljungdahl, 1953, Claus, 1956, Martindale, 1972, Steinegger and Hänsel, 1972, List and Hörhammer, 1972, Trease and Evans, 1978, British Pharmaceutical Codex, 1979, Blumenthal *et al*., 1990, Hänsel, 1992, Martindale, 1993, ESCOP, 2003, Braun, 2011) and are used for spasmodic gastro-intestinal complaints, flatulence, bloating and a sensation of fullness.

Table 2: Overview of historical data.

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Carum carvi L., fructus	Carminative	Oral use *Daily dose* 3 teaspoons (=12 g) to a glass of hot water to be drunk during the day	Madaus, 1938
		Oral *Usual dose* 1 g	Claus, 1956
		Oral use *Single dose* 0.5-2 g several times daily	Ljungdahl, 1953
	For spasmodic gastro-intestinal complaints, flatulence, and bloating.	Oral use *Single dose* 0.5-2 g several times daily	List and Hörhammer, 1972
	For dyspeptic problems such as mild, spastic condition of the	Oral use *Daily dose* 1.5-6 g of freshly crushed caraway	Blumenthal *et al*., 1990, Hänsel, 1992

	gastrointestinal tract, bloating and fullness.	fruit as an infusion or as another galenical preparations for internal use	
	Spasmodic gastro-intestinal complaints, flatulence, and bloating.	Oral use *Daily dose* 1.5-6 g of crushed caraway fruit as an infusion in 150 ml of boiling water (allow to stand for 10-15 minutes)	ESCOP, 2003
	For digestive complaints with mild cramps in the gastro-intestinal area, bloating, flatulence	Oral use 1.8 g crushed in 150 ml of boiling water 1-3 times daily	Braun, 2011
Essential oil obtained by steam distillation from the dry fruits of Carum carvi L.	Carminative.	Oral *Usual dose* 0.1 ml	Claus, 1956
		Oral use *Daily dose* 0.05-0.2 ml	Martindale, 1972, British Pharmaceutical Codex, 1979,
	For dyspeptic problems such as mild, spastic condition of the gastrointestinal tract, bloating and fullness.	Oral use *Single dose* 1-2 drops (equivalent to 0.05-0.1 ml) *Daily dose* 3-6 drops (equivalent to 0.15-0.3 ml)	Hänsel, 1992
		Oral use *Daily dose* 3-6 drops (equivalent to 0.15-0.3 ml)	Blumenthal *et al*., 1990

2.3. Overall conclusions on medicinal use

The traditional medicinal use of caraway fruit and caraway oil has been documented in several medicinal handbooks throughout a period of at least 30 years, including at least 15 years within the EU. Traditional medicinal use according to Directive 2004/24/EC is considered fulfilled for the symptomatic relief of digestive disorders such as bloating and flatulence. The strength and posology are summarised in table 3.

Table 3: Overview of evidence on period of medicinal use.

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Carum carvi L., fructus. Herbal substance or comminuted herbal substance as herbal tea for oral use.	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as bloating and flatulence. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	Oral use *Adolescents, adults and elderly Single dose* 0.5-2 g of the herbal substance or comminuted herbal substance in 150 ml of boiling water as a herbal infusion 1-3 times daily.	Since 1938 (Madaus, 1938, Ljungdahl, 1953, Claus, 1956, List and Hörhammer, 1972, Blumenthal *et al*., 1990,ESCOP, 2003, Braun, 2011) Poland before 1998, Germany since 1976
Essential oil obtained by steam distillation from the	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as bloating and	Oral use *Adults and elderly* *Daily dose*	Since 1956 (Claus 1956, Martindale

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
dry fruits of *Carum carvi* L. Herbal preparation in liquid dosage form for oral use.	flatulence. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	0.15-0.3 ml divided in 1-3 doses daily.	1972, British Pharmaceutical Codex, 1979, Hänsel, 1992, Blumenthal *et al*., 1990)
Essential oil obtained by steam distillation from the dry fruits of *Carum carvi* L. Herbal preparation for cutaneous use.	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as bloating and flatulence. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	Cutaneous use *Children, adolescent, adults and elderly* *Daily dose* 2% semi-solid preparations. To be applied once daily as a thin layer on the abdominal area.	Since 1976 in Germany

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Caraway fruit

There are several non-clinical *in vitro* studies reported on ethanolic caraway fruit extracts in different gastro-intestinal models. For example, there are reports from studies on intestinal smooth muscle cells of guinea pigs (Al-Essa *et al.*, 2010) and guinea pig ileum (ESCOP, 2003, Heinle *et al.*, 2006, Schemann *et al.*, 2006).

Table 4: Overview of the main non-clinical data.

Herbal preparation tested	Strength/ Concentration Dosage Route of administration	Experimental model *In vivo*/ *In vitro*	Reference Year of publication	Main non-clinical conclusions
Caraway fruit extract, 1 part drug to 3.5 parts ethanol, 31 % m/m	2.5 and 10.0 ml/l	*In vitro*: guinea pig ileum	(ESCOP, 2003)	antispasmodic activity
Caraway fruit extract, 1:2.5-3.5, extraction solvent: 30 % ethanol	Not available.	*In vitro*: guinea pig ileum	(Heinle *et al.*, 2006)	antispasmodic activity
Caraway fruit extract, 1:2.5-3.5, extraction solvent: 30 % ethanol	24-188 µg/ml	*In vitro*: stomach from guinea pig	(Schemann *et al.*, 2006)	increase in the mean antral contraction amplitude

Herbal preparation tested	Strength/ Concentration Dosage Route of administration	Experimental model *In vivo*/ *In vitro*	Reference Year of publication	Main non-clinical conclusions
Caraway fruit extract, 1:2.5-3.5, extraction solvent: 30 % ethanol	Not available.	*In vitro*: smooth muscle cells of the circular muscle layer of different parts of mouse intestine	(Sibaev *et al.*, 2006)	no effect on basic elecrophysiological properties
Caraway fruit extract, 1:2.5-3.5, extraction solvent: 30 % ethanol	Not available.	*In vitro:* intestinal 5-HT and muscarine M_3 receptors	(Simmen *et al.*, 2006)	no receptor affinity
Caraway fruit extract, extraction solvent: ethanol	2.5, 25 and 250 mg/ml	*In vitro*: dispersed intestinal smooth muscle cells of guinea pigs	(Al-Essa *et al.*, 2010)	decrease in the mean length of the smooth muscle cells was observed at 25 and 250 µg/ml

3.1.2. Secondary pharmacodynamics

Caraway fruit

Antimicrobial activity and antioxidant activity *in vitro* have been reported for ethanolic extracts of caraway fruit (ESCOP, 2003, Schempp *et al.*, 2006).

In a brine shrimp bioassay, the LC_{50} of an ethanolic caraway fruit extract was 85-266 µg/ml (ESCOP, 2003).

Aqueous and ethanolic extracts of caraway fruit have been tested in several *in vivo* models such as rat models of colitis (Keshavarz *et al.*, 2013) and gastric mucosal injuries (Khayyal *et al.*, 2001, Alhaider *et al.*, 2006, Khayyal *et al.*, 2006) The extracts reduced lesions when administrated orally or intraperitoneally at doses of 100-500 mg/kg (Khayyal *et al.*, 2001, Alhaider *et al.*, 2006, Khayyal *et al.*, 2006, Keshavarz *et al.*, 2013).

The effects of an aqueous caraway fruit extract on blood glucose and plasma lipids have been studied in *in vivo* models. Repeated oral doses of 20 mg/kg extract lowered blood glucose and triglyceride levels when administrated for two weeks to streptozotocin induced diabetic rats (Eddouks *et al.*, 2004, Lemhadri *et al.*, 2006). At an oral dose of 60 mg/kg for eight weeks to diet induced hyperlipidemic rats, changes in plasma lipid levels were observed (Saghir *et al.*, 2012).

Estrogenic effects have been reported from studies on aqueous and ethanolic extracts (defatted with petroleum ether) of caraway fruit in female rats. Oral doses of 150-300 mg/kg were administrated for 30 days. Results obtained indicate sequential changes in vaginal smear, increased ovary weight, increased uterus weight, decreased gonadotropins levels and increased estrogen levels. The estrogenic effects were observed from doses of ≥200 mg/kg for both extracts (Thakur *et al.*, 2009).

There are also results presented from studies on an aqueous extract in rats that showed an increase in urinary output at an oral dose of 100 mg/kg for eight days (Lahlou *et al.*, 2007) and renoprotective activity at an oral dose of 60 mg/kg for 60 days (Saghir *et al.*, 2012).

Caraway oil

Antimicrobial activity and antioxidant activity *in vitro* have been reported for caraway oil (ESCOP 2003, Hawrelak *et al.*, 2009, Samojlik *et al.*, 2010). Caraway oil has also been studied in the guinea pig tracheal smooth muscle *in vitro* model (ESCOP, 2003).

In *in vivo* models of colitis (Keshavarz *et al.*, 2013) and gastric mucosal injuries in rats (Baananou *et al.*, 2013), doses of 100-400 µl/kg or 100-300 mg/kg caraway oil reduced lesions when administrated orally or intraperitoneally.

Treatment of alloxan-induced diabetic rats at a dose of 10 mg/kg of caraway oil for six weeks reduced blood glucose and serum cholesterol (ESCOP, 2003).

Pretreatment with caraway oil at a dose of 130 mg/kg by gavage showed hepatoprotective activity in mice intoxicated with CCl_4 (Samojlik *et al.*, 2010).

d-Carvone

CNS-depressant effects in mice at doses of 50-200 mg/kg intraperitoneally have been reported, such as decrease in the response to the touch and ambulation, increase in sedation, palpebral ptosis, and antinociceptive effects. In potentiating pentobarbital sleeping time, l-carvone was more effective than d-carvone at a dose of 100 mg/kg, but was less potent at a dose of 200 mg/kg compared to the d-enantiomer (de Sousa *et al.*, 2007).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

The scientific literature contains numerous reports on non-clinical pharmacological studies of caraway fruit and caraway oil. None of the reported pharmacological studies constitute any cause for safety concern.

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

Caraway fruit

In the ESCOP monograph, it is described that the absorption of d-carvone from a caraway fruit extract (1:3, ethanol 30 % V/V) was tested in everted intestinal sacs prepared from male rats. At the concentration 117.4 µg/ml extract, the uptake was about 3 µg/cm^2 d-carvone after 30 minutes (ESCOP, 2003).

16 mg/kg of an oral dose of aqueous caraway fruit extract and 8 mg/kg of the butanol soluble constituents increased Cmax and AUC of rifampicin, pyrazinamide, and isoniazid in rats. A permeation enhancing property of the butanolic fraction across small intestinal absorptive surface (gut sac studies

ex vivo) was proposed to be a contributing factor in its bioavailability enhancing profile. The study concluded that the altered permeation characteristics were not due to any mucosal toxicity because there was no membrane damaging effect (Sachin *et al.*, 2009).

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

3.3.1. Single dose toxicity

Caraway fruit

No data available.

Caraway oil

In the ESCOP monograph, the acute oral LD_{50} of caraway oil in rats is reported from two different studies as 3.5 ml/kg and 6.7 g/kg (equivalent to 7.4 ml/kg), respectively. The acute dermal LD_{50} of caraway oil in rabbits was reported as 1.8 ml/kg (ESCOP, 2003).

d-Carvone

The LD_{50} (intraperitoneal) value in mice was 484.2 mg/kg (358.9–653.2) for d-carvone (de Sousa *et al.*, 2007).

Cited LD_{50} values for d-carvone were 1500 mg/kg for mice (intravenous), 1640 mg/kg for rats (oral), and 766 mg/kg for guinea pigs (oral) (NTP, 1990).

3.3.2. Repeat dose toxicity

Caraway fruit

No data available.

Caraway oil

No data available.

d-Carvone

The European Food Safety Authority (EFSA) Scientific Committee has published a safety assessment of d-carvone. In the assessment report, unpublished data from a 90-day NTP study in rats from the year 1982 is presented. The EFSA Scientific Committee concluded that relative liver weight of the surviving dose groups (93, 187 and 375 mg/kg) was statistically significantly increased compared with controls. The difference was present in both sexes, was dose-related and there was no dose without effect. Most animals from the two highest dose groups (750 and 1500 mg/kg) died during the study; those from the highest dose group were dead within 3 days of study start. Clinical signs recorded for these animals included hypoactivity, coat unkempt, piloerection, dehydration, excessive salivation, wet yellow stained anogenital region, impaired righting reflex, decreased grasping reflex, decreased limb tone, hypothermia, ataxia and prostration. From this study, the EFSA Scientific Committee established an ADI (acceptable daily intake) of 0.6 mg/kg bw/day for d-carvone, based on the 95% lower confidence limit for the benchmark dose response of 10% (BMDL10) of 60 mg/kg bw/day for an increase in relative liver weight and an uncertainty factor of 100 (EFSA, 2014).

In a study in rats, 1 % of d-carvone in the diet for 16 weeks was reported to cause growth retardation and testicular atrophy, while 0.1 % for 28 weeks and 0.25 % for one year had no effects (ESCOP, 2003).

According to the ESCOP monograph, WHO has established an ADI for d-carvone of 0-1 mg/kg/day based on short-term and long-term toxicity studies in rodents, including a no-observed-effect level (NOEL) of 93 mg/kg/day in rats (ESCOP, 2003).

In a 16-day study, mice that received 1600 or 3500 mg/kg of d-carvone by gavage five days per week died within seven days. Relative liver weights were increased for male mice and relative thymus weights were decreased for dosed female mice. No compound-related lesions were observed (NTP, 1990).

In a 13-week study, all male mice and 9/10 female mice that received the top dose of 1500 mg/kg of d-carvone five days per week died before the end of the study. No compound-related histopathologic changes were observed. At doses of 750 mg/kg, body weight, survival, or histopathology were not affected, but relative liver weights were increased (NTP, 1990).

Throughout a 2-year study in mice, body weights of male and female mice administered 375 or 750 mg/kg d-carvone five days per week for 103 weeks were similar to those of vehicle controls. Survival of dosed male mice was similar to that of vehicle controls, but survival of dosed female mice was greater than that of vehicle controls (NTP, 1990).

3.3.3. Genotoxicity

Caraway fruit

In a mutagenic screening (Ames test), a chloroform-methanol caraway fruit extract (10-100 mg/plate) showed an apparent increase in the number of *Salmonella typhimurium* strain TA 100 revertants in the presence of S9 mix (metabolic activation), but these observations were accompanied by a reduction in the background lawn of bacterial growth. This was also the result for other herbs, e.g. sage, celery seeds, star anise and nutmeg at 10-100 mg/plate. In the same test, no mutagenicity was observed with an aqueous caraway fruit extract up to 100 mg/plate (Rockwell and Raw, 1979).

Up to 75 mg/plate of caraway fruit as aqueous, methanolic and hexanic extracts was not mutagenic in Ames test with *S. typhimurium* strains TA 98 and TA 100 with and without metabolic activation (Higashimoto *et al.*, 1993).

An ethanolic caraway fruit extract at a concentration of 10 mg/plate was non-mutagenic in Ames test using strain TA98 and intermediately mutagenic in strain TA 102, without metabolic activation. In this study, an extract with less than 20 revertant colonies were considered inactive, 20-100 revertant colonies were considered mildly mutagenic, 100-200 revertant colonies were considered intermediately mutagenic, 200-500 revertant colonies were considered strongly mutagenic, and more than 500 revertant colonies per plate were considered very potent mutagenic agents. In the study, the most mutagenic extracts were derived from *Coriandrum sativum*, *Myristica fragrans, Eugenia caryophyllus* and *Zingiber officinalis* and they were considered strongly mutagenic (Mahmoud *et al.*, 1992).

An aqueous extract of caraway fruit at a concentration of 0.1 ml/plate (concentration not further specified) was not mutagenic in Ames test with *S. typhimurium strains* TA97a, TA98, TA100 and TA102 (Al-Bataina *et al.*, 2003).

Caraway oil

No data available.

d-Carvone

At concentrations up to 333 µg/plate, d-carvone was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with and without metabolic activation (NTP, 1990).

d-Carvone induced sister chromatid exchanges and chromosomal aberrations in mammalian cell test (Chinese hamster ovary cells) with and without metabolic activation at concentrations of 0.2-500 µg/ml. There was no correlation of dose with response (NTP, 1990).

3.3.4. Carcinogenicity

Caraway fruit

No data available.

Caraway oil

No data available.

d-Carvone

A 2-year carcinogenicity study were conducted by administering d-carvone by gavage to groups of 50 male and 50 female mice at doses of 375 or 750 mg/kg, five days per week for 103 weeks. Survival of dosed male mice was similar to that of vehicle controls; survival of dosed female mice was greater than that of vehicle control female mice. No neoplastic lesions attributed to d-carvone dosing were observed in mice (NTP, 1990).

In the ESCOP monograph carcinogenicity studies are reviewed. For example, in a feeding study with mice no carcinogenicity of d-carvone could be demonstrated. In another study, d-carvone administrated intraperitoneally to mice at doses of 6 and 1.2 g/kg three times per week for eight weeks caused no significant increase in lung tumours (ESCOP, 2003).

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Caraway fruit

No data available.

Caraway oil

In the ESCOP monograph it is cited that caraway oil applied to the backs of hairless mice produced no irritating effects. However, oil applied to intact or abraded rabbit skin was irritating. In addition, normal mice which had been sensitized 14 days previously by intraperitoneal injection of a caraway fruit extract showed an anaphylactic reaction when challenged on the abdominal wall by the same extract (ESCOP, 2003).

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Toxicological studies on caraway fruit and caraway oil are limited. The genotoxic potential of caraway fruit or caraway oil has not been fully evaluated. According to the current HMPC Guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/107079/2007)

the minimum requirement is a complete set of data from Ames test in five bacterial strains with and without metabolic activation.

There are toxicological data on the constituent d-carvone in mice from the National Toxicological Program (NTP), U.S., published in 1990. In the 16-day study at doses of 150 mg/kg and 723 mg/kg, relative liver weights were increased for male mice, although not in a dose-related manner. No compound-related lesions were observed. In the 13-week study relative liver weights were increased for both sexes at highest dose of 750 mg/kg. The survival rate or histopathology were not affected.

In the NTP study from 1990 on d-carvone it is also reported that sister chromatid exchanges and chromosomal aberrations were induced in a mammalian cell test with and without metabolic activation. NTP concluded that there was no correlation of dose with response. In addition, the NTP concluded that there was no evidence of carcinogenic activity of d-carvone for male or female mice administered 375 or 750 mg/kg by gavage for 2 years.

There are also toxicological data on the constituent d-carvone in rats from an unpublished NTP study that have been assessed by the European Food Safety Authority (EFSA) Scientific Committee in 2014. Despite many uncertainties with the data, the EFSA Scientific Committee decided to propose an ADI of 0.6 mg/kg bw/day for d-carvone based on an observed increase in relative liver weight. However, the EFSA Scientific Committee was unable to conclude whether the increase of liver weight was associated with the lethality observed in the higher doses. There was no histopathological evidence of liver toxicity, or any other information on a mechanism of liver toxicity of d-carvone.

The highest daily dose of caraway oil in the monograph is 0.3 ml, which corresponds to 273 mg of caraway oil (density 0.91 g/ml). According to the European Pharmacopeia, caraway oil should contain 50-65 % d-carvone (Ph. Eur. 01/2008:1817). For a person weighing 60 kg, the highest daily dose of d-carvone from using caraway oil in medicinal products corresponds to 3 mg/kg bw/day, i.e. five times above the ADI proposed by EFSA. The daily dose of d-carvone in the herbal tea of the monograph cannot be calculated, but is most probably much lower.

The available documentation (information from literature, products available on the market and valid registrations within the EU) show a long-standing and on-going medicinal use of caraway oil and caraway fruit in the EU. During this time, no signals of clinical safety concern have been identified in the literature or based on pharmacovigilance systems information (see section 5. Clinical Safety/Pharmacovigilance). Considering that the data from the NTP studies from 1982 in rats and 1990 in mice must be regarded inconclusive and that there are no signals of clinical safety concern during the long-standing use of caraway fruit and caraway oil, no safety concerns are raised against medicinal use of caraway fruit and caraway oil.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on caraway fruit or caraway oil to support the proposed indications are very limited. None of the reported pharmacological studies constitute any cause for safety concern.

Specific data on pharmacokinetics and interactions are not available. In an *in vivo* study, oral doses of caraway fruit extracts enhanced the plasma levels of rifampicin, pyrazinamide, and isoniazid in rats. The clinical relevance of these findings is not known.

Non-clinical information on the safety of caraway fruit or caraway oil is scarce. There are toxicological data on the constituent d-carvone in mice from the National Toxicological Program (NTP), U.S., published in 1990 and in rats from an unpublished NTP study in 1982 that have been assessed by the EFSA Scientific Committee in 2014. An increase in relative liver weight was observed in the 16-day

study in male mice at doses from 150 mg/kg and for both sexes at the highest dose of 750 mg/kg in the 13-week study. In rats, an increase in liver weight was observed from doses of 93 mg/kg. There was no histopathological evidence of liver toxicity, or any other information on a mechanism of liver toxicity of d-carvone from these two studies. Considering that the data from the NTP studies from 1982 in rats and 1990 in mice must be regarded inconclusive and that there are no signals of clinical safety concern during the long-standing use of caraway fruit and caraway oil, no safety concerns are raised against medicinal use of caraway fruit and caraway oil.

Genotoxicity, carcinogenicity, reproductive and developmental toxicology of caraway fruit or caraway oil have not been fully evaluated. Since the genotoxic potential of caraway fruit or caraway oil has not been fully evaluated, a European Union list entry cannot be recommended from a non-clinical point of view.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation 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

Caraway fruit

No data available.

Caraway oil

The effects on the motility of the stomach and gallbladder and on the orocaecal transit time of 50 mg caraway oil (WS 1520) orally have been studied in 12 healthy volunteers fasted for the previous 12 h. The study involved simultaneous ultrasonic determination of gastric and gall-bladder emptying, together with assessment of the orocaecal transit time using the lactulose H_2 breath test. In each volunteer, five investigations were performed on five different days, with a washout phase of at least 2 days after each investigation day. On the first day, placebo was given. On the following four investigation days, the four test substances 50 mg caraway oil (WS 1520), 90 mg peppermint oil (WS 1340), 10 mg cisapride and 10 mg n-butylscopolamine were studied in a randomized sequence. Subjects were blind to placebo and the test substances. The results showed that complete inhibition of gall-bladder emptying was caused by both oils and n-butylscopolamine. The orocaecal transit time was prolonged by peppermint oil and n-butylscopolamine, was not affected by caraway oil, and was shortened by cisapride (Goerg and Spilker, 2003).

The effect of an oral dose of 50 mg caraway oil (WS 1520) on gastro-duodenal motility was studied with stationary manometry in 8 healthy volunteers fasted for the previous 12 h. The study was a prospective, randomized, controlled and double-blind two period cross-over trial. The results showed that WS 1520 reduced the contraction amplitudes in the duodenum and reduced the contraction amplitudes and the duration of contractions in the gastric corpus during certain phases of the migrating motor complex (Micklefield *et al.*, 2003).

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

Caraway fruit

No data available.

Caraway oil

The pharmacokinetics of d-carvone and menthol after oral administration of an enteric coated formulation and immediate release formulation containing caraway oil and peppermint oil were studied in a randomized, two-period cross-over study in 16 healthy male volunteers. The subjects received 180 mg peppermint oil and 100 mg caraway oil once after 10 h fast. The pharmacokinetic data for d-carvone is presented in the table below (Mascher *et al.*, 2002).

Table 5. Pharmacokinetic parameters of d-carvone after oral administration of an enteric coated formulation and immediate release formulation containing 180 mg caraway oil (Mascher *et al.*, 2002).

d-Carvone	**Enteric coated formulation**	**Immediate release formulation**
AUC (ng/ml*h)	40.8±74.6	28.9±20.0
Cmax (ng/ml)	14.9±23.2	14.8±10.4
Tmax (h)	2.5±0.7	1.3±0.6
$t_{1/2}$ (h)	2.5±0.7	2.4±1.2

d-Carvone

A single low-dose of carvone (about 1 mg/kg) was ingested as a solution in full-fat milk (orally) in six volunteers (3 males; 1 smokers and 2 nonsmoker; and 3 females; 2 smokers and 1 nonsmoker). Urine samples were collected for 24 hours before (control) and after (test). Only a small amount of unmetabolised carvone was found in all test samples. The major metabolites of d- and l-carvone were identified as carvonic acid and uroterpenolone. Minor metabolites were identified as reduction products of carvone (i.e. carveol and dihydrocarveol). No difference in metabolism between d- and l-carvone were detected (Engel, 2001).

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data from clinical trials of adequate quality are available. Safety information from clinical studies is reviewed under section 5. Clinical safety.

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

There are insufficient data on clinical pharmacology or efficacy available for caraway fruit or caraway oil to support a well-established use indication.

Due to the finding that caraway oil caused a complete inhibition of gall-bladder emptying in healthy volunteers, it appears reasonable to include a warning to patients with obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases in section 4.4. of the monographs on caraway fruit and caraway oil.

5. Clinical Safety/Pharmacovigilance

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

Caraway fruit

No data available.

Caraway oil

Oral use

In a study on the effects on the motility of the stomach and gallbladder and on the orocaecal transit time at an oral dose of 50 mg caraway oil (WS 1520) in 12 healthy volunteers, no adverse events associated with the caraway oil treatment were observed (Goerg and Spilker, 2003).

No adverse events were observed during a study on gastro-duodenal motility at an oral dose of 50 mg caraway oil (WS 1520) in 8 healthy volunteers (Micklefield *et al.*, 2003).

A study investigated the weight lowering effects of caraway extract on physically active, overweight and obese women through a randomized, triple-blind, placebo-controlled clinical trial (n=35). The test samples were extracted from the fruits of caraway through steam distillation. From each 1 kg of caraway fruit, 10 litres of caraway water extract was produced. Consequently, the amount of caraway in terms of w/v was 0.1 (10%). Participants received either 30 ml/day of caraway extract or placebo orally for 3 months without changing their diet or physical activity. Subjects were examined at baseline and at week 12 for changes in body composition, anthropometric indices, and clinical and paraclinical variables. No changes were observed for heart rate, systolic and diastolic blood pressure, lipid profile, and urine-specific gravity. Of the sixty subjects who completed the study, there were 4 drop outs in the treatment group and 6 drop outs in the placebo group. No adverse events were reported from the treatment group (Kazemipoor *et al.*, 2013).

d-Carvone

Cutaneous use

In the ESCOP monograph it is cited that d-carvone did not produced any sensitization reaction in a test carried out on 25 volunteers at concentrations of 2 and 4 % in petrolatum (ESCOP, 2003).

5.2. Patient exposure

Aside from their market presence and data from a few studies in humans there are no data concerning patient exposure to caraway fruit or caraway oil when used in medicinal products.

Caraway fruit

Oral use

Caraway fruit is classified by the Council of Europe as a natural source of flavourings category 1, i.e. plant parts or products thereof, normally consumed as food items, herbs or species in Europe for which it is considered that there should be no restriction on use (Council of Europe, 2000).

Caraway oil

Cutaneous use

According to the European Commission database 'CosIng', which provides information on cosmetic substances and ingredients (contained in the Cosmetics Regulation EC No 1223/2009, Cosmetics Directive 76/768/EEC and Inventory of Cosmetic Ingredients), caraway oil can be used in cosmetics. There is no information available on safe doses of caraway oil in cosmetics.

d-Carvone

Oral use

In EU regulation on food flavouring, d-carvone is listed as food flavouring without restriction of use (EU regulation No 872/2012).

In the NTP report on d-carvone, it is cited that d-carvone was given generally-recognized-as-safe status by the Flavoring Extract Manufacturers' Association in 1965 and is approved by the Food and Drug Administration for use in food (Fed. Regist., 1961). An acceptable daily intake of 1.25 mg/kg was established for d-carvone by the Council of Europe in 1974 and by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives in 1967 (NTP, 1990).

5.3. Adverse events, serious adverse events and deaths

Enzyme immunoassay inhibition studies with a patient's serum revealed cross-reactivity among the IgE components from aniseed, caraway, coriander, and dill extracts (Garcia-Gonzalez *et al.*, 2002). In addition, positive skin prick tests and specific IgE to spices, especially those from the Apiaceae family, are more frequent in patients with allergy to mugwort pollen and birch pollen (Wuthrich and Hofer, 1984, Niinimaki *et al.*, 1995). (Garcia-Gonzalez *et al.*, 2002)

In the EudraVigilance database for the period up to February 2014, there were 10 spontaneous reports of suspected adverse drug reactions associated with *Carum carvi*. The reports were spread over several organ classes.

In the Vigisearch database of the World Health Organization's Uppsala Monitoring Centre for the period up to February 2014, there were 17 spontaneous reports of suspected adverse drug reactions associated with the single-ingredient *Carum carvi* and 7 reports for *Carum carvi*, oil. The reports were spread over several organ classes.

5.4. Laboratory findings

An extract produced by steam distillation of caraway fruit (1 kg of caraway fruit yielded 10 litres of caraway water extract) was given as an oral dose at 30 ml/day to physically active, overweight and obese women (n=35) for 3 months. Subjects were examined at baseline and at week 12 for changes clinical variables. No changes were observed for heart rate, systolic and diastolic blood pressure, lipid profile, and urine-specific gravity compared to placebo (Kazemipoor *et al.*, 2013). In a further evaluation of clinical variables the blood glucose, alanine aminotransferase, alkaline phosphatase, creatinine and blood parameters values were within normal clinical reference ranges (Kazemipoor *et al.*, 2014).

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Caraway fruit

The oral use in children and adolescents under 12 years of age has not been established due to lack of adequate data.

Caraway oil

Oral use

The oral use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Cutaneous use

Ointment after bathing and in the evening (10 g (=11.5 ml) ointment contains: 0.2 g caraway oil). To be applied once daily as a thin layer on the abdominal area.

5.5.2. Contraindications

Cross-allergy to plants within the Apiaceae family (nom. alt. Umbelliferaceae) associated with birch pollen and mugwort pollen allergy have been reported (Wuthrich and Hofer, 1984, Niinimaki *et al.*, 1995, Garcia-Gonzalez *et al.*, 2002, ESCOP, 2003) and should be included in section 4.3 of the monographs on caraway fruit (see also section 5.3 Adverse events, serious adverse events and deaths). Patients with known sensitivity to aniseed, celery, coriander, dill and fennel, or to other plants of the Apiaceae family should also avoid the use of caraway oil.

5.5.3. Special Warnings and precautions for use

The oral use of caraway fruit or caraway oil in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Caraway oil caused a complete inhibition of gall-bladder emptying in healthy volunteers. A warning to patients with obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases should be included in section 4.4. of the monographs of caraway fruit and caraway oil.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

There are no data on the use of caraway fruit or caraway oil as medicinal products during pregnancy and lactation in humans. The use of caraway fruit or caraway oil should not be recommended during pregnancy and lactation due to insufficient data. No data on fertility is available.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Conventional clinical safety data for caraway fruit and caraway oil are absent. However, there is a long-standing medicinal use and experience of caraway fruit and caraway oil documented within the EU in accordance with Directive 2004/24/EC (i.e. more than 30 years including at least 15 years within EU). Given the history of long-term and present use in humans, also in food and cosmetics, there are no safety concerns for the oral use of caraway fruit or the oral or cutaneous use of caraway oil.

Cross-allergy to plants within the Apiaceae family (nom. alt. Umbelliferaceae), to mugworth and to birch have been reported and should be included as contraindication in section 4.3 of the monographs on caraway fruit.

There are no safety concerns from the data collected on suspected cases of adverse drug reactions by the spontaneous reporting system since there are only a small number of reports and spread over several organ classes.

Caraway fruit cannot be recommended for oral use in children under 12 years of age due to lack of adequate data.

Caraway oil cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate data.

Caraway oil caused a complete inhibition of gall-bladder emptying in healthy volunteers. A warning to patients with obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases should be included in section 4.4. of the monographs on caraway fruit and caraway oil.

The use of caraway fruit or caraway oil should not be recommended during pregnancy and lactation due to insufficient data. There is no data on fertility available.

No data to recommend a specific limit to the duration of use is available, however as a general precaution related to the therapeutic indication, if symptoms persist longer than 2 weeks during the use, a doctor or a qualified health care practitioner should be consulted.

6. Overall conclusions

There is no documentation available for caraway fruit or caraway oil to support a well-established use indication.

The traditional medicinal use of caraway fruit and caraway oil has been documented in several medicinal handbooks throughout a period of at least 30 years, including at least 15 years within the EU. Traditional medicinal use according to Directive 2004/24/EC is considered fulfilled for oral administration of caraway fruit or caraway oil and cutaneous use of caraway oil for the symptomatic relief of digestive disorders such as bloating and flatulence and is plausible on the basis of long-

standing use and experience. The documented long-standing medicinal use may be considered as supported by limited results from pharmacological studies on the effect of caraway oil in the gastro-intestinal tract.

The experimental toxicological data are limited, but given the history of long-term and present use in humans, also in food and cosmetics, there are no safety concerns for the oral use of caraway fruit or the oral or cutaneous use of caraway oil. Traditional medicinal use according to Directive 2004/24/EC is considered fulfilled for oral administration of caraway fruit or caraway oil and cutaneous use of caraway oil for the symptomatic relief of digestive disorders such as bloating and flatulence.

However, as a general precaution related to the therapeutic indication, the product information should include a warning text advising the patient to see a doctor or a qualified health care practitioner if the symptoms worsen or persist longer than 2 weeks during the use of the product.

Caraway fruit cannot be recommended for oral use in children under 12 years of age due to lack of adequate data.

Caraway oil cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate data.

Cross-allergy to plants within the Apiaceae (Umbelliferaceae) family, to mugworth and to birch have been reported and should be included as contraindication in section 4.3 of the monograph on caraway fruit.

Caraway oil caused a complete inhibition of gall-bladder emptying in healthy volunteers and a warning to patients with obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases should be included in section 4.4. of the monographs on caraway fruit and caraway oil.

Reproductive and developmental toxicology of caraway fruit or caraway oil has not been fully evaluated. The use of caraway fruit or caraway oil should not be recommended during pregnancy and lactation due to insufficient data. No data on fertility is available.

Genotoxicity, carcinogenicity, reproductive and developmental toxicology of caraway fruit or caraway oil have not been fully evaluated. A European Union list entry is not supported due to lack of adequate data on genotoxicity for caraway fruit and caraway oil.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC. A typical analytical marker is d-carvone, which is used as a characteristic constituent for identification of caraway fruit and of caraway oil (Ph. Eur.).

In summary, it is recommended that monographs on *Carum carvi* L., fructus for oral use and *Carum carvi* L., aetheroleum for oral or cutaneous use are established with the following indication:

‘Traditional herbal medicinal product for the the symptomatic relief of digestive disorders such as bloating and flatulence.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.’

Therapeutic area: A03 AX Other drugs for functional gastrointestinal disorders

Annex

List of references