EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

Rapporteur(s)	E Svedlund
Peer-reviewer	A Assisi

HMPC decision on review of monograph *Carum carvi* L., fructus and aetheroleum adopted on July 2015	07 July 2015
Call for scientific data (start and end date)	From 1/2/2020 to 30/4/2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	18 November 2020

Review of new data on *Carum carvi* L., fructus and aetheroleum

Periodic review (from 2015 to 2020)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

The EudraVigilance database was searched on 4/6/2020 using the key words “caraway”, “carum”, “carvi”, and “carum carvi”.

☒ Scientific/Medical/Toxicological databases

Pubmed was searched on 12/6/2020 using the Mesh term “carum”. Cochrane database was searched 12/6/2020 using the key words “carway” and “carum carvi”. Embase database was searched 12/6/2020 using the key word “caraway”. ('caraway'/exp OR caraway) NOT caraway:au NOT ('black cumin'/exp OR 'black cumin') AND [2014-2020]/py.

☐ Other <Rapporteur to include text>

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

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Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

☒ Ph.Eur. monograph

☐ Other <Rapporteur to include text>

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other <Rapporteur to include text>

Other

☐ <Rapporteur to include text>

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒
Other	Yes	No

Summary and conclusions on the review

During the review 45 new references in PubMed and 248 new references in Embase not yet available during the first/previous assessment were identified.

No references were provided by Interested Parties during the Call for data.

15 references were considered to be relevant for the assessment.

0 references justify a revision of the monograph.

Revision is not recommended because there are no new data/findings of relevance for the content of the monograph.

Scientific data

Clinical efficacy

In a randomised controlled open-label cross-over trial, three treatment periods with hot caraway oil poultices (CarO) and hot olive oil poultice (OlivH) or nonheated poultices with olive oil (OlivC) as control interventions were investigated in patients with IBS (Lauch *et al.*, 2015). Patient blinding was not considered possible due to the characteristic smell of caraway oil and the heat. Patients were recruited through local newspaper and website advertisements. 48 patients with IBS (ROME III criteria) and at least moderate pain or discomfort were included in the study (40 females, 53.9±14.4 years). For the CarO, the patients were supplied with 2% essential oil of *Carum carvi* dissolved in olive oil and a mud-filled heat pad. Patients were instructed to embrocate a teaspoon of the solution on the abdominal area, place a moist and a dry towel over it and place the heat pad on the top, then rest for 20-30 minutes. Patients applied each intervention daily for 3 weeks followed by a 2 weeks 'wash-out' phase. After 3 weeks of use, they returned to the hospital, filled in questionnaires, and 2 weeks later, at the next visit, they were provided with the material and instruction for the next phase. The primary outcome was symptom severity (IBS-SSS). 37 patients completed the whole study. No patient resigned from the study due to adverse effects. One adverse event (gastrointestinal infection) was reported during the use of CarO. The authors report that a significant difference was found for symptom severity in favor of CarO compared to OlivC (difference –38.4, 95% CI –73.6, –3.1, p=0.033), but not compared to OlivH (difference –24.3, 95% CI –56.5, 7.9, p=0.139). According to the authors, the magnitude of the effect did not exceed the minimal, clinical important difference for the symptoms score on an average. Detailed information on other medication during the trial was not availabel. The authors conclude that hot caraway oil poultices appear safe, but the decrease in IBS symptoms may be a result of the heat application (Lauch *et al.*, 2015).

Assessor's comment:

This is a small, open-label study where the authors conclude that hot caraway oil poultices appear safe, but the decrease in IBS symptoms may be a result of the heat application. In addition, there is no information available that caraway oil as a single active substance has been in medicinal use within the EU for at least ten years for the treatment of IBS. Thus, this new clinical study does not introduce the possibility for the establishment of a well-establish use monograph.

Clinical safety

A 24 years old female patient with papillary thyroid carcinoma who had a history of near total thyroidectomy and was under therapy with 100 µg per day of levothyroxine experienced elevated TSH level (60.3 mIU/L) after ingestion of carraway and yarrow (Naghibi *et al.*, 2015). Before the intake of carraway and yarrow, her TSH level ranged from 0.07-0.3 mIU/L. The patient was also taking calcium carbonate 1000 mg/day and calcitriol 0.25 µg per day. The patient was not receiving any new medication and her drug regimen had not been changed during last 6 months. The only new food additive she was taking was caraway seed and yarrow. After discontinuation of the caraway and yarrow intake, her TSH level was decreased to normal range. This observation was assessed by

Naranjo causality index as a “possible adverse drug reaction” (score 3) while using WHO-UMC causality scale it was considered a “probable” ADR (Naghibi *et al.*, 2015).

Observing this change in TSH level, caraway capsules was produced and one of the researchers tried the medication on herself with a dose of 40 mg/kg per day. She was 24-years-old (weight=45 kg), with a history of hypothyroidism (autoimmune thyroiditis) for 5 years and taking 100 µg per day of levothyroxine. She was not taking any other medication. TSH level was between 2.5-3.7 mU/l in her medical records. Her initial TSH level before starting caraway was 2.3 mIU/L. She started to take caraway with dose of 1800 mg per day divided in 3 doses. Levothyroxine was ingested in fasting state in early morning and caraway capsules were used after each meal (breakfast, lunch and dinner). After 2 weeks, TSH level was 26 mIU/l and thyroid hormone levels were decreased indicating hypothyroid state (see Table 1 from Naghibi *et al.*, 2015 below). She continued using caraway capsules for 4 additional weeks when she started to complain from constipation. At the same time, TSH level increased to 110 mIU/L, and thyroid hormone level was further decreased (see Table 1 from Naghibi *et al.*, 2015 below). Thyroid exam was unchanged while she was in hypothyroid state both biochemically and clinically. Caraway was discontinued and thyroid values was measured after 2 weeks and showed TSH level of 25 mIU/L. Dose of levothyroxine was not changed and thyroid values were measured again 6 weeks after discontinuation of caraway. The TSH level further decreased to 11 mIU/l and T4-RIA level was increased to 9 ng/L (see Table 1 from Naghibi *et al.*, 2015 below). Two months later, TSH was further decreased to 7 mIU/l. The patient obtained 7 scores in Naranjo causality algorithm (probable ADR) and categorised as “certain ADR” in WHO-UMC score (Naghibi *et al.*, 2015).

Table 1 Hormonal levels in different time points after carum ingestion and discontinuation

	Carum ingestion			Carum discontinued	
Time	Beginning	2 weeks	6 weeks	8 weeks	12 weeks
TSH (mIU/L)	2.3	26	110	25	11
T4RIA (ng/L)	11	12	3.7	4.6	9
T3RIA (ng/L)	148	106	57	90	143
T3RU (%)	30	31	26	24	30

TSH = Thyroid stimulating hormone, T4RIA = T4 Radio-immuno-assay, T3RIA = T3-Radio-immuno-assay, T3RU = T3 Resin uptake.

The authors conclude that consumption of caraway increased TSH level in two hypothyroid patients using levothyroxine. The first patient was receiving caraway and yarrow while the second patient was receiving caraway only. The mechanism of action of this effect remains unknown (Naghibi *et al.*, 2015).

Assessor’s comment:

Naghibi et al., report that two hypothyroid patients on levothyroxine experienced elevated TSH levels after the intake of caraway. In both cases a positive dechallenge was reported.

However, the case report is from a non-EU country and it is not known if the herbal preparation in this case report corresponds to the herbal preparation in the monograph on caraway fruit. There are no case reports available on this possible interaction from the EU-market. Therefore, this single case report is considered not sufficient to trigger a revision of the monographs on caraway fruit or caraway oil.

Canabal *et al.*, 2016, report a case of anaphylactic shock in a pollen-allergic patient caused by a hidden allergen, caraway, which was not included in the list of ingredients on the product label. A 47-year-old woman was treated for anaphylactic shock with intramuscular adrenaline, antihistamine, and

intravenous corticosteroids and the patient fully recovered. The onset of the anaphylactic shock was 4 hours after eating scrambled eggs, blood sausage, and tuna dumplings with tomato sauce for dinner. Nonallergic anaphylaxis was ruled out. After thorough questioning, drugs, physical exercise, and alcohol were ruled out as cofactors in this episode. Other causes of anaphylaxis such as gastroallergic anisakiasis, hydatid disease, and mastocytosis were excluded. Serum tryptase levels measured several weeks after the anaphylactic reaction were within the normal range (5.6 µg/L). Pheochromocytoma and carcinoid syndrome were also ruled out. The ingredients listed on the blood sausage label were pork jowl, bacon, onion, pig's blood, and spices. The manufacturer provided a list of the spices (caraway, black pepper, paprika, cinnamon, nutmeg, clove, coriander, and marjoram). The results of skin prick tests (SPT) were positive to mugwort pollen (with a mean wheal diameter of 9 mm), *Cupressus arizonica* pollen (5 mm), *Lolium perenne* pollen (6 mm), pine nut, pistachio, and cat and dog dander. The results were negative for cereal flours, peach lipid transfer protein (LTP), egg, *Anisakis* species, oregano, cinnamon, onion, mustard, paprika, black pepper, nutmeg, lupine, and coriander. The SPT results from in-house spice extracts (10 mg/mL in phosphate-buffered saline) were positive for caraway (4 mm), coriander (3 mm), green aniseed (3 mm), cumin (3 mm), fennel (4 mm), histamine control (6 mm), and negative control (0 mm). Prick-by-prick tests were positive to caraway (3 mm) and negative to egg, raw and fried blood sausage, tomato sauce (all from the same brands as those consumed by the patient), cumin, clove, aniseed, and coriander. Total IgE was 47.90 kU/L and specific IgE measurements were positive for *C. arizonica*, *L. perenne*, mugwort pollen, and dog and cat dander. Determination of specific IgE (ImmunoCAP) to celery, aniseed, coriander, fennel, and caraway was negative in 2 tests. Specific IgE measurements using microarrayed allergens indicated positive results (medium-high) to mugwort LTP, nArt v3 (1 ISU), nArt v 1 (2.2 ISU), grass pollen group 1, major allergens from *C. arizonica,* rFel d 1*,* and rCan f 1. Determination of specific IgE to ω-5 gliadin (rTri a 19), animal serum albumins, and the remaining allergens was negative. The patient later tolerated pig meat, onion, eggs, blood sausage without spices, lamb, and beef. Allergenic proteins in caraway, coriander, and blood sausage were studied using IgE-immunoblotting and immunoblot-inhibition assays. Of the several allergenic bands observed, an IgE-binding band at 22 kDa was prominent. IgE binding was not observed when the allergens were incubated with a control serum. Immunoblotting inhibition showed that IgE binding to caraway extract was inhibited when the patient's serum was preincubated with blood sausage and vice versa. The patient was diagnosed with anaphylactic shock caused by caraway and coriander contained in blood sausage and sensitisation to other spices from the Apiaceae family. Subsequently, spices from this family were eliminated from her diet, and she has had no further anaphylactic reactions in the 5 years since then. The authors summarise that spices from the Apiaceae and Umbelliferae families, particularly aniseed, coriander, caraway, and celery, can induce severe allergic systemic reactions (Canabal *et al.*, 2016).

Assessor's comment:

This is a case report on anaphylactic shock after the intake of food containing several spices. The authors concluded that the reaction was caused by caraway and coriander in blood sausage and due to sensitisation of the patient to other species from the Apiaceae family. Hypersensitivity to the active substance, to other plants of the Apiaceae (Umbelliferae) family (fennel, anise, celery, coriander and dill), to mugwort or to birch has already been included as a contraindication in the monograph section 4.3.

In a review article by Spahn *et al.*, 2019, the authors present the presence of d-carvone in breast milk from results of the study by Denzer *et al.*, 2015 but also from two studies by Hausner *et al.*, 2008 and Hausner *et al.*, 2010. In the study by Denzer *et al.* 2105, 5 lactating mothers ingested 950 mL of fennel-anise-caraway tea on 3 test days each separated by more than 6 days. Milk was collected on a control day (prior to ingestion), and at 0.5, 1, and 2 h after ingestion. Mean concentration of predominant flavor components in 1 L of tea: limonene (associated with citrus flavor), 8.36±4.83

µg/L; 1,8-cineole, 1.24±0.53 µg/L carvone, 238±308 µg/L; trans-anethole, 858±1973 µg/L. There was a significant difference in concentrations across tea samples (cited in Spahn *et al.*, 2019). In the study by Hausner *et al.*, 2008, 18 lactating women ingested 4 capsules, 100 mg capsules of each: d-carvone (spearmint, caraway), l-menthol (mint), 3-methylbutyl acetate (banana, pear), trans-anethole (caraway, anise, fennel) on 3 separate test days (each separated by at least 3 days). Milk was collected at home before and 2, 4, 6, and 8 hours and ingestion on each test day. d-Carvone: milk concentrations peaked ~2 hours post ingestion and returned to baseline by 8 hours post ingestion; concentration (µg/L) at 0, 2, 4, 6, 8 hours: 1.33<7.17=5.61=4.30>2.66 (P<0.05). trans-Anethole: milk concentrations peaked ~2 hours postingestion and returned to baseline by 8 hours postingestion; concentration (µg/L) at 0, 2, 4, 6, 8 hours: 2.00<9.90=9.20=7.26>4.25 (P<0.05) (Spahn *et al.*, 2019). Sphan *et al.*, further present details on the study by Hausner *et al.*, 2010 where 40 lactating women (20 intervention group, 20 control group) ingested either 30 mg d-carvone/75 g hummus or 75 g plain hummus every third day for 28 days; milk collected 2 hours after ingestion on days 1 and 28. Detection of d-carvone in milk samples: d-carvone was detected in milk samples from 18 of 20 women in the experimental group (in 2 women it was detected in only 1 of 2 milk samples); detection rate was 83% (concentrations not significantly different after the first and tenth exposure). Mean±SEM d-carvone concentration in breast milk of women who ate caraway hummus: 3.2±1.0 µg/L; range: 0–13.2 µg/L; no d-carvone detected in milk samples from women who ate plain hummus (cited in Spahn *et al.*, 2019).

Assessor's comment:

There are several studies that show that d-carvone, one of the main constituents in caraway fruit and caraway oil, can be detected in breast milk after administration of d-carvone or fennel-anise-caraway tea in lactating women. In section 4.6 of the two monographs, the use of caraway fruit and caraway oil is not recommended during lactation and the information about the presence of d-carvone in breast milk will not change this recommendation. Thus, the information is considered not sufficient to trigger a revision of the monographs on caraway fruit or caraway oil.

Eudravigilance data

In the EudraVigilance database for the period up to June 2020, there were 40 spontaneous reports of suspected adverse drug reactions associated with *Carum carvi*. 21 reports were related to the oral use of combination products (20 in combination with peppermint oil and 1 report on a fennel-anise-caraway tea) and 18 cases were related to the rectal use in infants. There was only one non-serious report (diarrhoea) on caraway tea.

Assessor's comment:

There are no new safety concerns from the case reports in the EudraVigilance database up to June 2020.

Non-clinical toxicology

The safety profile of caraway oil have been evaluated by acute and repeated dose oral toxicity as per the OECD guidelines 423 and 407, respectively. In the acute toxicity study, a single dose of caraway oil (300 and 2000 mg/kg) was given to female Wistar rats, and the animals were observed for signs of behavioural alterations, morbidity and mortality for 14 days. A single oral dose at 300 mg/kg caraway oil did not show any signs of toxicity and mortality, while a dose of 2000 mg/kg showed signs of mortality in one animal and some signs of toxicity in another two animals. The repeated dose toxicity was performed at doses of 50, 100 and 200 mg/kg for 28 days in Wistar rats. The effects of caraway oil on food and water intake, body weight, relative organ weight, clinical biochemistry, hematological parameters and urine parameters were studied. Gross necropsy and histopathology of vital organs

were carried out. In the repeated dose toxicity study, caraway oil at selected dose levels did not show any significant alterations in food and water intake, body weight and relative organ weight. Administration of caraway oil did not show any significant changes in hematological, biochemical and urine parameters and histopathology study when compared with normal control animals (Auti and Kulkarni, 2019).

In 2015, the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA) initiated a re-evaluation of the safety of over 250 natural flavour complexes used as flavour ingredients. This procedure is applied in the re-evaluation of the generally recognized as safe (GRAS) status of natural flavour complexes with constituent profiles that are dominated by alicyclic ketones such as menthone and carvone, secondary alcohols such as menthol and carveol, and related compounds. The FEMA Expert Panel affirmed the GRAS status of caraway oil. The estimated daily intake of caraway oil from food sources is 140 μg/person per day (Cohen *et al.*, 2020). Cohen *et al.*, cite in their evaluation an OECD-compliant micronucleus assays on carveol and dihydrocarveol. Carveol and dihydrocarveol were not found to induce increases in the frequency of binucleated cells with micronuclei in cultured human peripheral blood lymphocytes (HPBL) in any treatment group. For carveol, the maximum dose levels selected for the micronucleus assay were 800 μg/mL for 4 hours exposure groups tested both with and without phenobarbitone/β-naphthoflavone-induced male rat liver S9 metabolic activation and 720 μg/mL for the 24 hours exposure group without S9 (Morris, 2014 cited in Cohen *et al.*, 2020). In another OECD-compliant study, d-Carvone showed no increase in mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2uvrA. The strains were incubated with d-carvone at concentrations up to 5000 μg/plate, in the presence and absence of phenobarbitone/β-naphthoflavone-induced rat liver S9 metabolic activation. Both the plate incorporation and pre-incubation methods were performed (ECHA, 2018, cited in Cohen *et al.*, 2020). Furthermore, d-carvone was negative in an OECD-compliant *in vitro* mammalian cell chromosome aberration assay in which human lymphocytes were incubated with d-carvone in the presence and absence of a S9 metabolic activation system prepared from phenobarbitone/β-naphthoflavone induced male rat liver. The dose ranges were 25–400 μg/mL for the 4 hours exposure without S9, 50–800 μg/mL for the 4 hours exposure with S9, and 12.5–400 μg/mL for the 24 hours exposure without S9. For all exposure groups, d-carvone did not induce any biologically relevant increases in aberrations in either the presence of absence of S9 metabolic activation (ECHA, 2018, cited in Cohen *et al.*, 2020). There is also one study that report that d-carvone was negative in an OECD-compliant mammalian cell forward mutation assay in L5178Y mouse lymphoma cells. Upon incubation with d-carvone at concentrations of 23–372 μg/mL for the 4 hours exposure without S9, 25–300 μg/mL for the 4 hours exposure with S9 and 3–100 μg/mL for the 24 hours exposure without S9, no significant increases in mutant frequency were observed both in the presence and absence of phenobarbitone/β-naphthoflavone-induced male rat liver S9 metabolic activation (ECHA, 2018, cited in Cohen *et al.*, 2020).

Assessor's comment:

There are no new safety concerns from the new non-clinical toxicology data.

Non-clinical pharmacology

In a non-clinical study by Mardani *et al.*, 2016, the effects of a 20% caraway hydroalcoholic extract (extraction solvent 75% ethanol) in a gel at doses of 500 and 1000 mg/kg was evaluated in oral mucositis in golden hamsters induced by 5-fluorouracil and cheek pouch scratching. The authors concluded that the caraway extract in a topical form may be associated with reduced intensity of oral mucositis (Mardani *et al.*, 2016).

In a study by Krueger *et al.*, 2020, the effects of peppermint oil and caraway oils on contractile and secretory activity in 255 human small and large intestinal preparations derived from surgical resections (73 patients) were studied. Peppermint oil and caraway oil concentrations dependently inhibited muscle contractility as indicated by sustained muscle relaxation and decrease in phasic contractility. These effects occurred in small and large intestinal preparations with IC_{50} values ranging between 17 and 90 µg/mL for peppermint oil and between 7 and 127 µg/mL for caraway oil. Neither peppermint nor caraway oil influenced the nerve evoked contractile response. The inhibition of contractile activity, but not the muscle relaxation, was prevented by the L-type calcium channel activator Bay K8644 but not by the neurotoxin tetrodotoxin. Both peppermint oil and caraway oil increased epithelial secretion, which remained in tetrodotoxin. The authors concluded that the findings showed a muscle inhibitory and prosecretory action of peppermint oil and caraway oils at clinically relevant concentrations (Kruger *et al.*, 2020).

The protective effect of an aqueous seed extract of caraway (50 mg/kg diet) on liver, kidney and reproductive organs in female rats against cadmium chloride intoxication have been reported. Toxic findings observed in liver and kidney with cadmium chloride treatment were found to be ameliorated after co-treatment with the caraway extract (Abdel-Wahab *et al.*, 2017).

Showraki *et al.*, 2019, evaluated whether the aqueous extract and essential oil of caraway seeds have anticonvulsant effects in mice. The anticonvulsant effects of the aqueous extract (200, 400, 800, 1600, and 3200 mg/kg, i.p.) and essential oil (25, 50, 100, 200, and 400 mg/kg, i.p.) of caraway were assessed using pentylenetetrazol (PTZ; 95 mg/kg i.p.) induced convulsions. Diazepam (3 mg/kg) was used as positive control. The latency time before the onset of myoclonic, clonic, and tonic convulsions and the percentage of mortality were recorded. In addition, the effect of caraway on neuromuscular coordination was evaluated using the rotarod performance test. The extract and essential oil dose-dependently increased the latency time to the onset of myoclonic (ED_{50} of 1257 and 62.2 mg/kg, respectively) and clonic (ED_{50} of 929 and 42.3 mg/kg, respectively) seizures. The extract and essential oil of caraway prevented the animals from tonic seizure with ED_{50} of 2142.4 and 97.6 mg/kg, respectively. The extract and essential oil of caraway protected 28.6 and 71.4% of the animals from PTZ-induced death, respectively, and had no significant effect on neuromuscular coordination (Showraki *et al.*, 2016).

To examine the effects of caraway seeds on blood levels of glucose, lipid profile, and C-reactive protein in streptozotocin induced diabetic male Wistar rats, doses of 1 g/kg and 2 g/kg caraway was administered as aqueous extract orally once a day for 3 weeks. Diabetic rats receiving 1 and 2 g/kg caraway extracts had significantly lower total cholesterol, low-density lipoprotein, non- HDL-C, LDL-C to HDL-C ratio and atherogenic index than that of diabetic control rats. Moreover, there were significant changes in fasting blood glucose in diabetic groups treated with 1 and 2 g/kg caraway extracts compared with the diabetic control. However, caraway did not have any significant effect on C-reactive protein level in diabetic rats (Sadjadi *et al.*, 2014).

Assessor's comments:

There are no safety issues from the cited non-clinical studies on caraway fruit or caraway oil.

Combination products

There are several reports from clinical trials and meta-analysis on the efficacy of combination products with caraway oil, mostly in combination with peppermint oil. For example, there are several clinical studies on the combination of caraway and peppermint oil in patients with functional dyspepsia (Rich *et al.*, 2017; Chey *et al.*, 2019; Li *et al.*, 2019), but also in patients with irritable bowel syndrome (IBS) (Madish *et al.*, 2019).

Assessor's comments:

There are no safety issues raised from the studies on combination products with caraway oil.

References

a) References relevant for the assessment:

Abdel-Wahab A, Hashem Abdel-Razik AR, Abdel Aziz RL. Rescue effects of aqueous seed extracts of Foeniculum vulgare and Carum carvi against cadmium-induced hepatic, renal and gonadal damage in female albino rats. *Asian Pacific Journal of Tropical Medicine* 2017, 10(12):1123-1133

Auti ST, Kulkarni YA. Acute and 28-day repeated dose oral toxicity study of caraway oil in rats. *Drug Metabolism and Personalized Therapy* 2019 (Abstract only)

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Chey WD, Lacy BE, Cash BD, Epstein M, Corsino PE, Shah SM. A novel, duodenal-release formulation of a combination of caraway oil and l-menthol for the treatment of functional dyspepsia: A randomised controlled trial. *Clinical and Translational Gastroenterology* 2019, 10(4):1-9

Cohen SM, Eisenbrand G, Fukushima S, Gooderham NJ, Guengerich FP, Hecht SS, *et al*. FEMA GRAS assessment of natural flavor complexes: Mint, buchu, dill and caraway derived flavoring ingredients. *Food and Chemical Toxicology* 2020, 135 (Article Number 110870):1-32

Krueger D, Schäuffele S, Zeller F, Demir IE, Theisen J, Michel K, *et al.* Peppermint and caraway oils have muscle inhibitory and pro-secretory activity in the human intestine *in vitro*. *Neurogastroenterology and Motility* 2020, 32(2):1-9

Lauche R, Janzen A, Lüdtke R, Cramer H, Dobos G, Langhorst J. Efficacy of Caraway Oil Poultices in Treating Irritable Bowel Syndrome - A Randomized Controlled Cross-Over Trial. *Digestion* 2015, 92(1):22-31

Li J, Lv L, Zhang J, Xu L, Zeng E, Zhang Z, Wang F, Tang X. A Combination of Peppermint Oil and Caraway Oil for the Treatment of Functional Dyspepsia: A Systematic Review and Meta-Analysis. *Evidence-based Complementary and Alternative Medicine* 2019, Article Number 7654947:1-9

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Mardani M, Afra SM, Tanideh N, Andisheh Tadbir A, Modarresi F, Koohi-Hosseinabadi O, *et al*. Hydroalcoholic extract of Carum carvi L. in oral mucositis: A clinical trial in male golden hamsters. *Oral Diseases* 2016, 22(1):39-45

Naghibi SM, Ramezani M, Ayati N, Zakavi SR. Carum induced hypothyroidism: An interesting observation and an experiment. *DARU, Journal of Pharmaceutical Sciences* 2015, 23(Article Number 5):1-5

Rich G, Shah A, Koloski N, Funk P, Stracke B, Köhler S, *et al*. A randomized placebo-controlled trial on the effects of Menthacarin, a proprietary peppermint- and caraway-oil-preparation, on symptoms and quality of life in patients with functional dyspepsia. N*eurogastroenterology and Motility* 2017, 29(11 Article Number e13132):1-9

Sadjadi NS, Shahi MM, Jalali M-T, Haidari F. Short-term caraway extract administration improves cardiovascular disease risk markers in streptozotocin-induced diabetic rats: A dose-response study *Journal of Dietary Supplements* 2014, 11(1): 30-39

Showraki A, Emamghoreishi M, Oftadegan S. Anticonvulsant effect of the aqueous extract and essential oil of Carum carvi L. seeds in a pentylenetetrazol model of seizure in mice. *Iranian Journal of Medical Sciences* 2016, 41(3): 200-208

Spahn JM, Callahan EH, Spill MK, Wong YP, Benjamin-Neelon SE, Birch L, *et al*. Influence of maternal diet on flavor transfer to amniotic fluid and breast milk and children's responses: A systematic review. *American Journal of Clinical Nutrition* 2019, 109:1003S-1026S

b) References that justify the need for the revision of the monograph:

None.

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on *Carum carvi* L., fructus and aetheroleum, by consensus.