European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *FOENICULUM VULGARE* MILLER SUBSP. *VULGARE* VAR. *VULGARE*, AETHEROLEUM' EMEA/HMPC/263292/2006

Table 1: Organisations that commented on the document as released for consultation on 25 October 2006 until 28 February 2007

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	European Forum for Complementary and Alternative Medicine (EFCAM)
3.	European Federation of Associations of Health Product Manufacturers (EHPM)
4.	Kooperation Phytopharmaka, Germany

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Table 2: Discussion of comments

General comments	Comment and rationale	Rapporteur's comments
	It is not clear to us why a draft monograph on sweet fennel oil has not been prepared in parallel with that on bitter fennel oil. In view of potential differences in composition of the oils, we accept that separate monographs would be necessary, but both oils are used medicinally. In fact, sweet fennel oil was used in a recent clinical study in primary dysmenorrhoea [Namavar 2003]	A decision was taken to prepare a Community herbal monograph for each European Pharmacopoeia monograph concerning herbal substances/herbal preparations of fennel. Because up to now the European Pharmacopoeia monograph on sweet fennel oil does not exist and the information on the preparations marketed in Europe refers to bitter fennel oil, only the monograph on bitter fennel oil has been prepared.

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4.1 Therapeutic indications	From our point of view, the following indications are suitable for a well-established medicinal use: ▪ Dyspeptic complaints such as mild spasmodic gastro-intestinal ailments, bloating, flatulence. ▪ Catarrh of the upper respiratory tract. These indications are justified by the following references: CZYGAN 2002, BRAND 1993, WEISS 2002. Clinical experience and expert opinions are available as well as supportive pharmacological data which thus meet the requirements for the well-established medicinal use.	Published clinical data are insufficient to support the well established use. References mentioned by IPs reinforce rather the plausibility of the traditional use.
4.2. Posology and method of administration	For the **well-established medicinal use** we propose the same posology as the one currently indicated for the "traditional use". These recommendations are justified by the references mentioned under "indications. We suggest deleting the paragraph restricting the use in children and adolescents. For the reasons given under 5.3 such a restriction is not justified. Fennel oil is used for the production of fennel honey, a preparation commonly used in children. Furthermore, no adverse effects were apparent in a recent controlled clinical study in the treatment of infantile colic, in which an emulsion of 0.1% fennel oil in water (5-20 ml, up to 4 times daily for 7 days, with a fennel oil limit of 12 mg/kg/day), orally administered to babies 2-12 weeks of age, was found effective [Alexandrovich 2003]. The use of fennel oil preparation in children from 3 months upwards should be considered acceptable, subject to suitable dosage scheme this should be similar to one recommended for fennel fruits and provide amounts of diluted fennel oil comparable to those found in the respective infusions from this fruits, bearing in mind that only about 10% of the oil from fennel fruit passes into an infusion [Fehr 1982]. **Duration of use:** A limitation of use to two weeks cannot be deduced from preclinical data (see 5.3.), hence we recommend replacing the current statement by **"no restriction"**	Not agreed. The well established use is not supported by sufficient scientific data. The Alexandrovich's clinical study is discussed in the assessment report. The investigations available in human beings on the role of fennel in reducing pain in infantile colic are very preliminary, while safety data on the use of fennel oil in children are lacking. There are reasons of concerns due to the presence of compounds such as trans-anethole and estragole, known to be mutagenic/carcinogenic according to non-clinical data. Thus the HMPC does not recommend the use of a THMP in such sensitive population groups, considering that THMPs have to be safe in the conditions of use Moreover, because of the lack of available safety data even on long-term use of fennel preparations, a limit of two weeks is consistent with a self-medication indication, which is the case for a THMP. If symptoms persist or worsen after two weeks it is necessary to consult a doctor.

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4.4 - Special Warnings and Precautions and 4.5 Interactions Monographs and list entries)	The IPs question whether it is appropriate, in proportion to the perceived possible danger, to mention the cross-reactivity risk to Asteraceae. In absence of any documented evidence, the IPs propose to delete the statement in section 4.4.	Endorsed.
4.4 - Special Warnings and Precautions and 4.5 Interactions with other medicinal products and other forms of interaction	IPs also recommend taking out the statement on the potential influence on hormone therapy or oral contraception (cf. comments under 5.3). In the absence of human data, (see 4.5), the proposed warning/precaution in 4.4 would not appear to be justified, and they question whether it is appropriate, in proportion to the perceived possible danger.	Not endorsed. Estrogenic properties of fennel extracts and trans-anethole, the major constituent of fennel oil, have been described by different authors. It cannot be excluded that excessive doses could influence hormone therapy or oral contraception. For the safe use of fennel oil preparations we deem useful to give a warning on this risk.

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4.6. Pregnancy and lactation	The 1st paragraph states: *"There are no data from the use of fennel oil in pregnant patients"*. We recommend replacing this sentence by the following: *"Clinical data on the safety of using fennel oil preparations in pregnancy are lacking. Therefore, pregnant women are recommended to seek advice from their healthcare professional before taking fennel oil preparations."* Reasons: In this context we would like to refer to our comments on section 5.3. Furthermore, it has to be considered which alternatives pregnant women do have to treat bloating and related intestinal symptoms which they do frequently experience during pregnancy. In the **2nd paragraph** the following wording is proposed by the HMPC: *"Studies in animals have shown reproductive toxicity of trans-anethole and fennel oil"*. For the reasons given under section 5.3, we propose to **delete this statement**. For the same reasons, we recommend to delete the statement not to use anise oil in childbearing potential without effective contraception. With regard to the assessment of estragole, we propose to delete the last sentence *"In the absence …"* for the following reasons: According to the HMPC draft, chapter 5.3., fennel oil contains only low amounts of estragole. Furthermore the content of estragole is restricted by the European Pharmacopoeia. The HMPC *Public Statement on the Use of Herbal Medicinal Products Containing Estragole* (EMEA/HMPC/137212/2005) recommends to minimize, not to exclude the "exposure of estragole to sensitive groups such as young children, pregnant and breastfeeding women". Such a minimisation is already done by the European Pharmacopoeia.	Not endorsed The sentences reported in the monograph are in agreement with the statements in annexes I and III of the 'Guideline on SPCs' and the template for a Community herbal monograph EMEA/HMPC/107436/05 Rev. 2 Although clinical safety data on use of fennel oil in pregnancy are lacking, according to the recommendations of the HMPC Public statement on the use of herbal medicinal products containing estragole, "the exposure of estragole to sensitive groups such young children, pregnant and breastfeeding women should be minimised". See section 5.3 See overview of comments on anise oil (endorsed). The limits for the estragole content set by the European Pharmacopoeia are considered to be quality limits rather than safety limits for minimising the exposure of sensitive groups.

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4.7. Effects on ability to drive and use machines	We propose to say: "No data available."	Not endorsed. The sentence is in compliance with the template for a Community herbal monograph EMEA/HMPC/107436/05 Rev. 2
4.8. Undesirable effects	We suggest to delete "and gastro-intestinal system" because there are no reports available.	Endorsed.
5.3. Preclinical safety data	The 2nd paragraph of the HMPC draft states: *"For trans-anethole anti-implantation, early abortifacient and antifertility activity has been reported in rats"*. We would like to comment on this statement as follows: **a) Studies on reproduction/developmental studies** In the study of DHAR (1995), 50, 70 or 80 mg/kg trans-anethole (not defined) were given on day 1-10 of pregnancy (n=6/treatment), a reduction of the number of the implantations sites by 33, 66 or 100 %, respectively, was described. In further experiments anethole was administered on day 1-2 or on day 3-5 of pregnancy. An antifertility effect was observed only by treatment on day 3-5, application on day 1 and 2 was uneffective. Malformations were not observed. These findings are in clear contrast to those cited in NEWBERNE et al, 1999. The FEMA GRAS Assessment of trans-anethole does not show any hints on adverse effects of the substance on fertility or reproduction although trans-anethole was studied in three experimental sets. Doses from 0, 25, 175 or 350 mg/kg b.w. were given by gavage to rats (n=10/treatment) starting on day 7 prior to mating up to day 4 of lactation. Only in the highest dose group a slight increase of gestation time, increases in pup mortility and stillbirths and reductions of body weight of the pups were noted. No gross physical abnormalities were associated with anethole treatment.	The sentence related to the estrogenic and antifertility activity of trans-anethole demonstrated in vitro and in laboratory animals at high concentrations has been modified, specifying that it is not considered relevant to human exposure given the recommended posology and conditions of use. Experimental data cited by the IPs are included in the assessment report. Despite the lack of human data, they do not exclude potential toxicity of trans-anethole and fennel oil at higher doses and for prolonged use, especially for sensitive population groups such as children, pregnant and breastfeeding women. On the contrary, experimental conditions showed a) reduction in the number of the implantation sites causing antifertility effect, b) increasing of gestation time, pup mortality and stillbirths, reduction of body weight of the pups. Although some of these effects were noted at highest doses, they do not support fennel oil safety in pregnancy.

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5.3. Preclinical safety data	In a four generations study in rats (n=40), anethole was added at a concentration of 1% to the diet (corresponding to 700 mg/kg b.w.). The only effect observed was a reduced body weight and a reduced body weight increase in the pups. In a further experiment, this delay in the growth of the pubs could be explained by the reduced palatability of trans-anethole. The authors concluded that trans-anethole did not produce any reproductive toxicity at doses which are not associated with palatability problems (LE BOURHIS 1973, cited in JECFA 1999). The findings of the publication of DHAR seem to be of questionable relevance. They are in clear contrast to those cited in NEWBERNE et al, 1999. who described three independent investigations (ARGUS (1992, cited in JECFA 1999, JECFA 1999, LE BOURHIS 1973, cited in NEWBERNE et al. 1999). These investigations have been performed in a sufficient number of animals and in a very elaborated and correct way and therefore are regarded to be reliable. The very weak effects seen in these well-conducted and documented experiments even in excessive doses of anethole up to 1400 mg/kg b.w./day clearly put a question mark behind the results of DHAR (1995) who reports a 100% inhibition of implantation at a dose of 80 mg/kg b.w./day administered p.o., i.e., 50% of the NOEL which had been determined with 175mg/kg b.w./day (ARGUS RESEARCH LABORATORIES 1992, cited in NEWBERNE et al. 1999 and JECFA 1999). The author does not adequately describe the quality and source neither of the anethole used in the study nor of any other material. Figures in the paper do not indicate standard deviations. The reported increase of implantation inhibition from 33% at 50 mg/kg b.w. to 66% at 70 mg/kg and to 100% at 80 mg/kg appears rather drastic for a biological effect. Furtehrmore, the number of animals per group (n=5) was rather small.	Some works cited (Argus, Le Bourhis) are not relevant to support a clear safety of trans-anethole because original data are not accessible and the studies are not mentioned in the most important data banks. Works mentioned in the assessment report, even if carried out with a limited number of animals, are the only factual source of anise and anethole toxicity. On the contrary all the other criticisms are until now the result of personal opinions.

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5.3. Preclinical safety data	Thus two extensive, well-documented studies (ARGUS 1992 and LE BOURHIS 1973, both cited in JECFA 1999) suggest that anethole, the major constituent of aniseed oil, is safe during pregnancy and lactation for both mothers and offspring. The study of DHAR (1995) suggests a strong anti-implantation effect of anethole but is very poorly documented. Teratogenic effects were not observed in any of the studies. **b) Estrogenicity of anethole** For trans-anethole an estrogenic activity has been discussed on the basis of in vitro findings and animal experiments. The assumption of an estrogenic activity is based on mainly older reports, starting with a study of ZONDEK and BERGMANN (1938) who describe anise oil to be estrogenic in the Allen-Doisy-test (200µl/day for seven days, s.c.). In 1980 ALBERT-PULEO conducted studies with anise oil and compounds isolated after exposing the oil excessively to oxygen and UV light. The authors considered desmethyl-anethole and polymerisation products of anethole to be responsible for the observed activity. In an attempt to verify the hypothesis that stilbene-like dimerisation products of anethole exhibit estrogen-effects, KRAUS and HAMMERSCHMIDT (1980) subjected fennel oil (>80% anethole) to extreme storage conditions in terms of light, oxygen and temperature. These authors did not detect any anethole dimers in the so-treated oil. MIETHING et al (1990), however, found 0.39ppm of 4,4´-dimethylstilbene in aniseed oil exposed to daylight for 6 months. The authors concluded that the dimer was a reaction product of anethole and anisaldehyde. The fact that isolated anethole is practically free of anisaldehyde is a likely explanation for the contradictory results of different authors. From these findings it can be concluded that an estrogenic activity observed in older experiments may be due to compounds which result from inappropriate storage. Thus storage has to be performed under appropriate conditions in accordance with the European Pharmacopoeia.	Trans-anethole estrogenic activity has been demonstrated both in animals (Dhar, SK., 1995) and in humans (Howes MJ et al., 2002). Both the works are discussed in the assessment report. Miething found the dimer 4,4´-dimethylstilbene in aniseed oil. The contradictory work of Kraus and Hammerschmidt is a Company report not published in journals subjected to reviewers. In conclusion to date estrogenic activity of anethole is a possible not still cleared risk for people using products containing anethole.

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5.3. Preclinical safety data	**Receptor binding studies** In two papers, results on the estrogenic activity of trans-anethole in yeast cells were published: TABANACA et al (2004) observed an estrogenic activity with an IC_{50} value of 625 µg/ml, as compared to 17β-estradiol, the effectivity was 8.6 x 10^{-8}. HOWES et al (2002) observed an estrogenic activity of trans-anethole only at a concentration of 10 mM, i.e. at a concentration of 1.48 mg/ml (corresponding to 1.48 g/l). Lower concentrations studied were ineffective. From these findings it can be concluded that an interference of trans-anethole with hormone therapy or oral contraceptives can be expected only at unrealistic high and clinically not relevant concentrations of the substance: in order to obtain an IC_{50} value according to TABANACA et al (625 mg/l), an intake of at least 2.5 g would be necessary, according to HOWES et al even a higher intake of 6 g per volunteer. **In vitro findings** The metabolism and the metabolites which were formed at different concentrations of trans-anethole were investigated in isolated rat hepatocytes by NAGAKAWA and SUZUKI (2003). At a weakly toxic concentration (0.5 mM) trans-anethole was mainly metabolized to 4-methoxycinnamic acid (4MCA), 4-hydroxy-1-propenylbenzene (4OHPB) and to the monosulfate conjugate of 4OHPB. Free unconjugated 4OHPB reached less than 0.5 µM, whereas at the toxic concentration of 1 mM unconjugated, free 4OHPB reached 10 µM. It seems to be of special interest that the rate of formation of free unconjugated 4OHPB, a minor metabolite, is only relevant at high toxic concentrations. The authors showed that only the free unconjugated metabolite 4OHPB formed from anethole by *O*-demethylation is responsible for the estrogenic effects of anethole, i.e, for the receptor binding as well as for the stimulation of the growth of MCF-7 cells (estrogen receptor positive mammary carcinoma cells). Receptor binding was observed with IC_{50} values of 5 x 10^{-5} M for 4OHPB, whereas neither anethole nor its metabolite 4MCA showed interference with 17β-estradiol receptor binding up to a concentration of 10^{-3} or 10^{-4} M, respectively. 4OHPB stimulated cell proliferation of MCF-7 cells in a range of 10^{-6} to 10^{-8} M, whereas neither anethole nor its metabolite 4MCA showed any effect.	Experiments of **Tabanca** et al., reported an IC_{50} value of 625 µg/ml. They refer to Pimpinella anisum fruit oils, not to fennel (Tabanca et al 2004 Estrogenic activity of isolated compounds and essential oils of Pimpinella species from Turkey, evaluated using a recombinant yeast screen Planta Med. 2004; 70:728-35). The study of Howes (2002) confirming that high concentrations of trans-anethole have the potential to interact with estrogen receptors in rodents, leads to suggest caution with the use of fennel oil in human sensitive population groups. Conclusions of the Nakagawa and Suzuki's experiments, based on studies on rodents, are the following "These results suggest that the biotransformation of anethole induces a cytotoxic effect at higher concentrations in rat hepatocytes and an estrogenic effect at lower concentrations in MCF-7 cells based on the concentrations of the hydroxylated intermediate, 4OHPB".

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5.3. Preclinical safety data	The authors concluded that 4OHPB is responsible for the estrogenicity of anethole. The metabolism of trans-anethole in human volunteers has been studied (NEWBERNE et al 1999, CALDWELL 1987). In contrast to rodents there was no clear dependency of the dose on the rate and the route of elimination (doses of 1, 50 or 250 mg anethole were applied). Elimination was much faster in humans than in rodents. 8 hours after application the bulk of the dose was eliminated in expired air and urine of men, whereas in rats or mice it took 48-73 hours in high doses. 13-17 % of the metabolites in urine of the volunteers were *O*-demethylation products. Thus it obvious that neither in mice nor in rats a satisfying testing of anethole toxicity is possible; especially at higher doses the pronounced differences in metabolism may result in an overestimation of the possible risk (CALDWELL 1987). **In vivo-studies** In one study a significant increase in uterus weight of juvenile rats was seen following application of 80 mg/kg b.w. for three days (DHAR, 1995). The relevance of this finding is questionable since the findings on a possible anti-fertility activity of the author were not confirmed by other, more reliable studies (NEWBERNE et al, 1999). **For these reasons a restriction of use of Fennel oil in children and adolescents as well as in pregnant and breastfeeding women and during childbearing potential appears to be inappropriate. While for reasons of general precaution fennel oil should be used during pregnancy only after consultation of a physician, general restrictions for the other groups do not seem appropriate in the light of available data.** Estragole as a minor constituent does not seem to be of high relevance. As the content of estragole is limited by the pharmacopoeia monograph, we suggest including a respective statement under 5.3.	To date very little is known about the metabolism of trans-anethole by humans. Caldwell's research group published two articles on metabolism of trans-anethole in humans, both including essentially the same experiments (Sangster, Caldwell et al., 1987; Caldwell and Sutton, 1988). The fundamental conclusion of the authors is only that "the pattern of urinary metabolites of trans-anethole is unaffected by dose size". Any consideration on risk influence is lacking. These Caldwell's experiments show essentially the difference in anethole metabolism between rodents and humans. The work of Dhar is a scientific article reporting original experiments. The Newberne's article, discussed in the assessment report, is an assessment of studies on anethole not reporting new original experiments. As discussed in the assessment report, the body of scientific data indicates that reproductive system is a target for the action of fennel extracts and its principal constituent trans-anethole. Changes in male and female organs and tissues involved directly or indirectly in the reproductive mechanisms have been described in laboratory animals. Consequences of these changes are not easily predictable or detectable and they cannot definitely be excluded in humans. Therefore the use of a self-prescription THMP such as fennel oil in sensitive population groups cannot be recommended, due to the lack of complete safety data. The remark on the estragole content is covered by the footnote 1: The material complies with the Ph. Eur. monograph.