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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON *FOENICULUM VULGARE* MILLER SUBSP. *VULGARE* VAR. *VULGARE*, AETHEROLEUM

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Comments should be provided using this template to hmpc.secretariat@emea.europa.eu
Fax: +44 20 7523 7051

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

DRAFT COMMUNITY HERBAL MONOGRAPH ON *FOENICULUM VULGARE* MILLER SUBSP. *VULGARE* VAR. *VULGARE*, AETHEROLEUM

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished products.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended i) Herbal substance: not applicable ii) Herbal preparation: *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum (Bitter fennel fruit, oil)

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
	Herbal preparation in solid or liquid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
	Traditional herbal medicinal product used as an expectorant in cough and cold. The product is a traditional herbal medicinal product for use in specified indication exclusively based on long-standing use.

[1] The material complies with the Ph. Eur. monograph.

[2] The declaration of the active substance(s) should be in accordance with relevant herbal quality guidance.

4.2. Posology and method of administration

Well-established use	Traditional use
	Posology *Adults* 0.2 ml of essential oil, as a single dose per day or in multiple divided doses. The use in children and adolescents is not recommended due to the lack of adequate data for safety assessment and because of the presence of estragole. **Method of administration** Oral use. **Duration of use** Not to be taken for more than two weeks. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

4.3. Contraindications

Well-established use	Traditional use
	Known hypersensitivity to the active substance or to Apiaceae (Umbelliferae) (**aniseed, caraway, celery, coriander, dill and fennel)** or to anethole.

4.4. Special warnings and precautions for use

Well-established use	Traditional use
	Patients with known hypersensitivity to Asteraceae (Compositae) should avoid the use of fennel and its preparations, because of cross-reactivity risk. Because its oestrogenic activity, excessive doses of fennel oil may affect hormone therapy, oral contraceptive pill and hormone replacement therapy (see sections 4.5 and 5.1).

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
	Excessive doses of preparations containing fennel oil may affect hormone therapy or oral contraception (see section 4.4). If the patient is on other medications he/she should seek medical advice (see section 4.4).

4.6. Pregnancy and lactation

Well-established use	Traditional use
	There are no data from the use of fennel oil in pregnant patients. Studies in animals have shown reproductive toxicity of trans-anethole and fennel oil (see section 5.3). Therefore fennel oil is not recommended in pregnancy and in women of childbearing potential not using effective contraception. It is unknown if fennel oil constituents are excreted in human breast milk. The excretion of fennel oil constituents in milk has not been studied in animals. In absence of sufficient data and because of the presence of estragole whose exposure should be minimised in pregnant and breastfeeding women, it is preferable to avoid the use of fennel oil preparations during pregnancy and lactation.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
	No studies on the effect on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Well-established use	Traditional use
	Allergic reactions to fennel oil, affecting the skin, the respiratory and gastro-intestinal system, may occur. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

4.9. Overdose

Well-established use	Traditional use
	No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended. The traditional medicinal use of fennel oil has been largely due to its antispasmodic, secretolytic, secretomotor and antibacterial effects. Bronchodilatory effect of fennel oil is partly due to a potassium channel opening effect. Secretolytic and expectorant effects may be due to the content of anethole and fenchone.

5.2. Pharmacokinetic properties

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended. No data available for fennel oil in human beings or animals. After oral administration the compound trans-anethole is rapidly absorbed. 54-69% of the dose is eliminated in the urine and 13-17% in exhaled carbon dioxide. Trans-anethole is reported to be metabolised by O-demethylation and by oxidative transformation of the C3-side chain. The bulk of elimination occurred within 8 hours. The principal metabolite is 4-methoxyhippuric acid.

5.3. Preclinical safety data

Well-established use	Traditional use
	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product. For trans-anethole anti-implantation, early abortifacient and antifertility activity has been reported in rats. Trans-anethole is reported as "generally recognised as safe" (GRAS) at the intake of 54 µg/kg body weight/day). The acceptable daily intake (ADI) of trans-anethole established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) should not exceed 2 mg/kg body weight. Fennel oil was found to be mutagenic. Results from studies carried out in laboratory animals showed a weak mutagenic activity of anethole. Estragole is a minor constituent of fennel oil. Several studies have shown the carcinogenic effects of estragole and some of its metabolites in mice (mainly malignant liver tumors). The EMEA/HMPC assessment[3] is that the profiles of metabolism, metabolic activation and covalent binding of estragole are dose-dependent and tend markedly to decrease at low levels of exposure (less than linear decrease with respect to dose); according to this assessment, rodent studies indicate that these events are probably minimal in the dose range 1-10 mg estragole/kg b.w., which is approximately 100-1000 times the anticipated human exposure to this substance from traditional diet and as added flavouring substance. Investigations showing liver enzymes-inducing effects of compounds present in fennel oil raise the possibility for interactions of fennel with other medicinal products to take place.

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use
	Not applicable.

7. DATE OF COMPILATION/LAST REVISION

26 October 2006

[3] Please refer to the HMPC Public statement on the use of herbal medicinal products containing estragole (EMEA/HMPC/137212/2005).