European Medicines Agency
Evaluation of Medicines for Human Use

London, 15 September 2006
Doc. Ref: EMEA/HMPC/263273/2006

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON *PIMPINELLA ANISUM* L., AETHEROLEUM

DISCUSSION IN MLWP	May 2006 September 2006
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	7 September 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	2 January 2007
ADOPTION BY HMPC	
PUBLICATION OF FINAL MONOGRAPH	

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

KEYWORDS	Herbal medicinal products; HMPC; Community herbal monograph; traditional use.

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 *PIMPINELLA ANISUM* L., AETHEROLEUM

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished products.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1]

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: *Pimpinella anisum* L., aetheroleum (anise oil)

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
	Herbal preparation in solid or liquid dosage forms for oral use (to be described according to the standard terms published by the European Pharmacopoeia).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

[1] The material complies with the Ph. Eur. The declaration of all active substances should be as expressed in the Guideline on the Quality of herbal medicinal products/traditional herbal medicinal products, CPMP/QWP/2819/00 Rev 1 and EMEA/CVMP/814/00 Rev 1. and if relevant, type of extracts should be specified as defined in the general monograph on Extracts of the Ph. Eur. (ref 765).

Well-established use	Traditional use
None	i) Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence. ii) Traditional herbal medicinal product used as an expectorant in cough and cold. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.

4.2. Posology and method of administration

Well-established use	Traditional use
	Adults: Indication i): 0.05-0.2 ml of anise oil, three times daily. Indication ii): 0.05-0.2 ml of anise oil, three times daily 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. **Duration of administration** Not to be taken for more than two weeks. **Method of administration** Oral use. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

4.3. Contraindications

Well-established use	Traditional use
	Patients with known sensitivity to Apiaceae (Umbelliferae) (**fennel, caraway, coriander and dill**) or to anethol.

4.4. Special warnings and precautions for use

Well-established use	Traditional use
	Patients with known sensitivity to Asteraceae (Compositae) should avoid the use of anise oil, because of cross-reactivity risk. Because of the oestrogenic activity of anethol, as a precautionary measure, anise oil preparations should be avoided during hormone therapy, oral contraceptive pill and hormone replacement therapy (see section 4.5).

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

Well-established use	Traditional use
	Estrogenic activity of trans-anethol has been demonstrated in vitro and in the laboratory animals, but not in humans. For this reason preparations containing anise oil might affect hormone therapy or oral contraception in women (see section 4.4).

4.6. Pregnancy and lactation

Well-established use	Traditional use
	There are no data from the use of anise oil in pregnant patients. Studies in animals have shown reproductive toxicity of trans-anethol (the major constituent of anise oil) (see section 5.3). Therefore anise oil is not recommended in pregnancy and in women of childbearing potential not using effective contraception. It is unknown if anise oil constituents are excreted in human breast milk. The excretion of anise 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 anise 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 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
	Ingestion of 1 to 5 milliliters of anise oil has been associated with nausea, vomiting, seizures and pulmonary oedema.

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 anise oil has been largely due to its antispasmodic, secretolytic, expectorant and antibacterial effects. Anise oil exerts spasmolytic effects on smooth muscles of different organs (tracheal, jejunum and ileum) by antagonising the activity of contraction-inducing agents. Secretolytic and expectorant effects may be due to the content of anethol in the essential oil. Anise oil exerts bronchodilatory effects *in vitro*. Anise oil, as well as some oil components, exhibit *in vitro* inhibitory activities against the growth of a wide spectrum of bacteria and fungi known to be pathogenic for man and other species. Trans-anethol content of anise oil may be responsible for oestrogenic activity.

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 anise oil in human beings or animals. After oral administration the compound trans-anethol is rapidly absorbed. 54-69% of the dose is eliminated in the urine and 13-17% in exhaled carbon dioxide. Trans-anethol is reported to be metabolized 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-anethol at high doses (50, 70, 80 mg/kg body weight) dose-dependent anti-implantation, early abortifacient and antifertility activity has been reported in rats. Trans-anethol is reported as "generally recognized as safe" (GRAS) at the intake of 54 μg/kg body weight/day). The acceptable daily intake (ADI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is 0-2 mg/kg body weight. Ethanolic aniseed extracts are mutagenic at high concentrations. Results from studies carried out in the laboratory animals showed a weak mutagenic potential of anethol. Estragole is a minor constituent of anise oil. Several studies have shown the carcinogenic effects of estragole and some of its metabolites in mice (mainly malignant liver tumors). The EMEA/HMPC (2005) assessment 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.

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use

7. DATE OF COMPILATION/LAST REVISION

7 September 2006