EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum (EMA/HMPC/534924/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum as released for public consultation on 15 March 2011 until 15 June 2011

	Organisations and/or individuals
1	AESGP

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Caryophylli aetheroleum-containing products, should facilitate mutual recognition in Europe. We have the following specific comments.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1 Therapeutic indications	AESGP	We suggest adding as a 3rd indication "traditional herbal medicinal product for the support of digestive functions." **Reasons** The combination product esto-gast® contains clove oil (Caryophylli aetheroleum) Ph.Eur. (0.0235 g per 100 g) with the indication “traditionally used for the support of digestive functions." Proof of tradition The product has been marketed in Germany since 1910. It is a combination of four essential oils and corresponds to the monograph "Spiritus melissae compositus, Karmelitergeist" of the German Pharmacopeia 6th Edition (DAB 6) of 1926.	Not endorsed. The Community herbal monograph on *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum does refer to the traditional medicinal use of clove essential oil as the only active ingredient in products. Combination products can be considered, if reasonable, for safety issues only, but not for the establishment of indications.

		Karmelitergeist is also described in the German health authority's list of traditionally used substances and combinations according to section 109a of the German medicines law (current position number 32). Karmelitergeist has been continuously described in the German Pharmacopeia from its 1st edition issued in 1872 until its 6th edition of 1926 which was reprinted in 1952. The product esto-gast® is still nowadays produced according to the rules of DAB 6. Fischer and Hartwich ("Hagers Handbuch" 1919) mention Karmelitergeist as a well-known product which is also internally used for (digestive) stimulation. The Rote Liste of 1939 describes gastrointestinal complaints as indications for the use of Karmelitergeist. All these documents prove a far more than 30-year tradition of Karmelitergeist for the support of the digestive functions and thus demonstrate the traditional use of clove oil in this indication. The following documents are attached: Deutsche Pharmakopoe, Hager, 1872 Pharmacopoea Germanica, 1892 Deutsches Arzneibuch, 5. Ausgabe 1910 Deutsches Arzneibuch, 6. Ausgabe 1926 Hagers Handbuch der Pharmazeutischen Praxis, 1919 Rote Liste, 3. Aufl., 1939 <u>Plausibility of pharmacological effects</u> Furthermore, the following new references demonstrate a plausible activity of clove oil in gastrointestinal complaints and for support of digestive functions: In the experiment of Agbaje (2008)[1], a hot aqueous extract	

		of cloves showed several gastrointestinal effects in the rat. The review of Chaieb (2007)[2] describes several biological activities of clove oil. Positive effects of eugenol, one of the main compounds of clove oil, were described by Hollander (1949)[3] and Morsy (2008)[4] who investigated mechanisms of the gastroprotective effect of this substance. The histological study of Hollander [3] demonstrated changes in the gastric mucous barrier resulting from the repeated application of an aqueous eugenol emulsion to dogs. Morsy [4] investigated possible mechanisms underlying the gastroprotective effect of eugenol against indomethacin-induced ulcer in rats. Gastric ulceration was induced by a single (i.p.) injection of indomethacin (30 mg/kg). Pretreatment with a single dose of eugenol (100 mg/kg, orally), 1 hour before indomethacin administration caused significant reductions in gastric mucosal lesions, gastric acid outputs and pepsin activity associated with a significant increase in mucin concentration. Additionally, eugenol significantly attenuated the elevations in gastric mucosal malondialdehyde and total nitrite, and the decrease in reduced glutathione observed with indomethacin. The authors concluded that an anti-ulcer effect of eugenol is mediated by opening of K(ATP) channels, scavenging free radicals, decreasing acid-pepsin secretion, increasing mucin production and preventing a deleterious rise in nitric oxide level. Taguchi (2005)[5] showed that oral intake of a clove preparation taken as a herbal food may suppress an overgrowth of *Candida albicans* in the intestinal tract. Braun (2007) [6] found expression of four olfactory receptors in human mucosal enterochromaffin cells. Ca^{2+} imaging studies revealed that odorant ligands of the identified olfactory	

		receptors, e.g. eugenol and isoeugenol cause Ca^{2+} influx, elevation of intracellular free Ca^{2+} levels and consequently serotonin release. As serotonin controls both gut motility and secretion and is involved in pathologic conditions such as vomiting, diarrhoea and irritable bowel syndrome, the authors concluded that olfactory receptors are potential novel targets for the treatment of gastrointestinal diseases and motility disorders. A traditional use of clove oil for support of the digestive functions is described on various websites [7], excerpts of which are attached as a copy. **Thus the pharmacological effects with regard to the support of the digestive functions of clove oil are plausible on the basis of longstanding use and new publications. For these reasons, inclusion of a 3rd indication "traditional herbal medicinal product for the support of digestive functions" is justified.**	