EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2012
EMA/HMPC/44043/2012
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Zingiber officinale* Roscoe, rhizoma (EMA/HMPC/749154/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on Zingiber officinale, rhizoma as released for public consultation on 15 August 2011 until 15 November 2011

	Organisations and/or individuals
1	European Scientific Cooperative on Phytotherapy (ESCOP)
2	European Botanical Forum (EBF)
3	Kooperation Phytopharmaka (KOOP Phyto)
4	The Association of the European Self-medication Industry (AESGP)
5	Professor emeritus Dr. Dr. Robert Anton

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
ESCOP	We welcome the preparation of a Community draft monograph on Zingiber officinale Roscoe (ginger) and would like to make the following comments.	
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Zingiberis rhizoma-containing products, should facilitate mutual recognition in Europe. We have the following specific comments, in particular on the paragraph on the use in pregnancy and lactation.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1. Therapeutic indications	ESCOP	**Traditional use** Indication 1 **Comment** The general term 'motion sickness' is best applied across all of those stimulus-specific terms such as car-sickness, air-sickness, sea-sickness, space-sickness, etc. [Golding JF. Motion sickness susceptibility. Autonomic Neuroscience: Basic and Clinical 2006; 129:67-76]. **Proposed change** Traditional herbal medicinal product for the symptomatic relief of motion **or** motion/travel sickness.	Agreed and changed accordingly into motion sickness.
4.2. Posology and method of administration		**Traditional use** Indication 1 **Comment** The HMPC draft assessment report (page 5/49) lists 'ZINTONA-Kapseln' (250 mg/capsule) which have been	The product has not been on the market for 30 years. The patient leaflet for "Zintona-Kapseln" is the only one of the traditionally used ginger products that has an

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		available since 1983 [ESCOP Monograph 2009-reference 48] with an MA in Austria since 1987, ie. the product has been on the market almost 30 years. **Proposed change** *Adolescents, Adults and Elderly:* 500 or 750 mg half an hour before travelling and depending on severity, 500 mg every four hours thereafter. Do not exceed 2 g in total per day. *Children between 6 and 12 years of age:* 250 or 500 mg half an hour before travelling and depending on severity, 250 mg every four hours thereafter. Do not exceed 1 g in total per day. **Justification:** ZINTONA patient leaflet. **and** *[Schmid R, Steffen R, Tschopp A, et al. Which one of seven commonly used agents is best for prophylaxis of seasickness? J Travel Med 1994; 1: 203-6].*	indication for repeated dosages. This is not in itself an argument for recommending repeated dosage therapy. Repeated dosage therapy for motion sickness rests on shaky grounds, since only 1 low-quality randomised studies (the study of Careddu 1999 in children) has used this treatment modality. In the study by Schmid *et al*. 1994 in adults, it is unclear whether this treatment modality was used. No maximum tolerable dosage has been established. Moreover the study by Schmid *et al.* cannot support a traditional dosage.
4.4. Special warnings and precautions for use		**Comment** Infants and very young children are immune to motion sickness and susceptibility only begins around 6 or 7 years of age [Golding JF. Motion sickness susceptibility. Autonomic Neuroscience: Basic and Clinical 2006; 129:67-76].	This is a point with diverse opinions. First of all it has to be recognised that one of the referred randomised studies included children 4 years of age with a history of motion sickness (Careddu 1999). Some text books in medicine and other reviews suggest that all age groups – even toddlers – can experience motion sickness, and, further, that children 2-12 years of age are the most susceptible. Even if it were true that children below 6 years of age are not susceptible to motion sickness, a warning is necessary.

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4.6. Pregnancy and lactation		Ginger is commonly used during pregnancy (under medical supervision) [ESCOP Monograph 2009] **and** the Assessor's Comment [EMA/HMPC/577856/2010] states "*a well established use of ginger root in the prevention of pregnancy-induced nausea and vomiting is suggested".* **and** "ginger is a safe, effective and inexpensive solution for treating nausea and vomiting of pregnancy (NVP) and should be considered as a first-line option for management of NVP symptoms, or as adjuvant with other forms of therapy". [Ebrahami N, Maltepe C, Einarson A. Optimal management of nausea and vomiting of pregnancy. Int J Womens Health 2010; 2: 241-8]	It is correct that prospective clinical studies have not found a higher incidence of adverse pregnancy outcomes with ginger treatment; however only a moderate number of exposed pregnant women (n =490) have been included in the prospective studies and in general treatment duration has been short. Recommendation of up to 10 weeks treatment with ginger based on studies of 3-7 days is not possible. Findings in the few experimental animal studies performed of advanced skeletal development and increased embryo resorption with high dose ginger administration are difficult to interpret, however such findings are not totally inconsequential. Although they do not seem to suggest any definitive concerns with respect to reproductive and developmental safety of ginger root, it is the HMPC´s opinion that the usage of ginger in pregnancy is not to be advocated, due to the small number of pregnant women included in the prospective studies, the limited outcome analysis and the short treatment duration, coupled with the adverse findings in animal studies, along with the minor clinical benefit in pregnancy-induced nausea and vomiting.
4.1. Therapeutic indications	EBF	**Traditional use** Indication 1) "Traditional herbal medicinal product for the symptomatic relief of travel sickness." to be amended by proposed change. Proposed change (if any): "Traditional herbal medicinal product for the symptomatic relief	With respect to ginger use in pregnancy, see comment above. The use of ginger to reduce risk of postoperative nausea and vomiting administered shortly before induction of anaesthesia is not compliant with commonly agreed surgical and anaestesiological

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		of travel sickness, including the prophylaxis of the nausea and vomiting of motion sickness of pregnancy (under medical supervision). As a postoperative antiemetic for minor surgical procedures" (Rationale ESCOP 2nd Ed. Suppl.2009 p.290 et 2nd Ed.2003 p.547)	guidelines that patients undergoing elective surgery should fast 6 hours from solids and 2 hours from liquids to reduce the risk of aspiration. Consequently, a general recommendation to administer ginger before surgery cannot be recommended.
4.6. Pregnancy and lactation	KOOP PHYTO	The draft monograph states that safety during pregnancy and lactation has not been established and, in the absence of sufficient data, the use during pregnancy and lactation is not recommended. **From our point of view the statement on pregnancy should be deleted.** The textbook of Schäfer states that ginger products are used in pregnancy, preferably in the first trimenon. The textbook refers to the studies which are quoted e.g. in the monograph of ESCOP and which are available to the HMPC, e.g. Vutyavanich et al 2001 and Fischer-Rasmussen 1999 (included in the HMPC reference list). The textbook therefore expressively recommends the use of ginger in pregnancy.	With respect to ginger use in pregnancy, see comment above.
4.6 Pregnancy and lactation	AESGP	The draft monograph states that safety during pregnancy and lactation has not been established and, in the absence of sufficient data, the use during pregnancy and lactation is not recommended. From our point of view the statement on pregnancy should be deleted because there is sufficient clinical data available on the use of ginger preparations during pregnancy, and there is no evidence of any potential harmful effects.	With respect to ginger use in pregnancy, see comment above.

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		The ESCOP monograph even includes a dosage recommendation for nausea and vomiting of pregnancy (75 mg to 2 g daily in divided doses for 1 to 5 days under medical supervision). This recommendation is based on various references [1-4] which are already quoted in the HMPC reference list. The HMPC draft Assessment Report states that prospective clinical studies (involving 490 women) did not find a higher incidence of adverse pregnancy outcomes with ginger treatment, and experimental animal studies did not seem to suggest any definitive concerns with respect to reproductive and developmental safety of ginger. However, the draft Assessment Report comes to the conclusion not to advocate the use of ginger in pregnancy although possible consequences for adverse foetal development cannot be deduced from the available studies. We do not concur with this conclusion, as clinical benefit in nausea and vomiting has been demonstrated. In this context, the HMPC draft Assessment Report does indeed state that in randomized controlled studies the efficacy of powdered ginger has been demonstrated in pregnancy-induced nausea and vomiting by several studies at a dosage of 500 mg 3 times daily and a treatment duration of 3-5 days. Several studies in pregnant women justify the deletion of the recommendation not to use ginger during pregnancy. - In detail, Fischer-Rasmussen et al. [1] demonstrated in a randomized, double-blind, cross-over study involving 27	

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		pregnant women that powdered ginger given orally as 4 × 250 mg daily for 4 days gave significantly greater relief of the symptoms of hyperemesis gravidarum than placebo (p = 0.035). - Keating and Chez [2] performed a randomized, double-blind, placebo-controlled study in 26 women less than 12 weeks pregnant to evaluate the efficacy of ginger syrup containing 250 mg of ginger or placebo four times daily for 2 weeks. - In the randomized, double-blind study of Vutyavanich et al. [3], 70 women at various stages of pregnancy up to 17 weeks of gestation took 4 × 250 mg of ginger or placebo daily for 4 days. Compared to the placebo group significant reductions in severity of nausea (p = 0.014) and episodes of vomiting (p<0.001) were reported in the ginger group. - In the randomized single-blind study of Ozgoli et al. [4], 67 pregnant women at less than 20 weeks of gestation who had complained of mild to moderate nausea with or without vomiting, were treated with 4 × 250 mg of ginger daily or placebo for 4 days. From the evaluation of VAS questionnaires completed daily by the patients, the severity of nausea decreased significantly in more ginger users than placebo users (84% versus 56%; p<0.05). The number of vomiting episodes experienced by the ginger users declined to a significantly greater extent than in the women who received placebo (50% versus 9%; p<0.05). - In another double-blind study of the effectiveness of ginger in the treatment of nausea 120 women less than 20 weeks	The study did not assess pregnancy outcome. Due to the small number of patients no statistical analysis was performed. No analysis of the pregnancy outcome was performed in the study. No analysis of the pregnancy outcome was performed.

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		pregnant were randomized to receive 4 × 125 mg of a ginger extract (equivalent to 4 × 1.5 g of ginger) or placebo daily for 4 days [5]. From clinical practice, many gynaecologists/obstetricians recommend to their pregnant women with nausea and/or vomiting the intake of ginger alone or in dietary complements with vitamins and minerals [11][12][13] Ginger is on the FDA Generally Recognised As Safe list http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=786bafc6f6343634fbf79fcdca7061e1&rgn=div5&view=text&node=21:3.0.1.1.13&idno=21) With regard to the mechanism of action underlying ginger's antiemetic activity is not yet clearly understood but the aromatic, spasmolytic, carminative and absorbent properties of ginger suggest it has direct effects on the gastrointestinal tract. [14] Furthermore, several randomized, double-blind studies have compared ginger with vitamin B6 in the treatment of nausea and vomiting of pregnancy [6-9]. Moreover, in the systematic review of Pittler and Ernst [10], in comparison with placebo no adverse reactions to ginger were noted. All these studies support our comment that ginger should not be contraindicated during pregnancy.	

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	Professor emeritus Dr. Dr. Robert ANTON	**Nature of the problem:** There are some discrepancies in the conclusions of the two documents, especially the restriction of use present in the monograph does not reflect exactly the interpretation and the result of analysis of the scientific literature presented by the Assessor. **Elements from the Community herbal monograph** *4.6. Pregnancy and lactation: "safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended".* **Elements of assessment report and conclusions of the expert on *Zinziber officinale* Roscoe, rhizome EMA/HMPC/577856/2010 :** "***there is a plausible scientific evidence from several randomized clinical studies that oral intake of encapsulated dry powdered rhizome from Zinziber officinale is better than placebo and non-inferior to some commonly used antiemetics in ameliorating pregnancy-induced nausea and vomiting and could be proposed for well-established use. The dosage may be 500mg 3 times daily for 3-5 days."*** On a clinical point of view, ginger modifies in single dosages of 1000-2000 mg the gastric muscular contractions and increases the gastric emptying. The number of patients treated in meta-analyses is important. Indeed, the number of pregnancy-induced nausea and vomiting patients in randomized studies is not negligible and acceptable (675, 30, 70, 26, 138, 120, 209, 126, 170, 70 patients). All the results show that ginger is	With respect to ginger use during pregnancy, see comment above It should be added that the conclusion in the AR the comment reads: "Prospective studies have not found a higher incidence of adverse pregnancy outcomes. **However, it has to be stressed that treatment durations have been short and only a moderate number of patients have been included in the prospective studies.**" And further in the overall conclusion: "Prospective clinical studies have not found a higher incidence of adverse pregnancy outcomes with ginger treatment; **however treatment durations have generally been short and only a moderate number of exposed pregnant women (n =490) have been included in the prospective studies."**

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		effective at a dosage between 1000 and 1500 mg during mostly 3-4 days and higher than a placebo. Consequently, the assessor went to the conclusion that "***according to the general guideline of clinical documentation, a well established use of ginger root in the prevention of pregnancy-induced nausea and vomiting is suggested***." Concerning the safety during pregnancy observed in a clinical study on 187 patients, the conclusion is that ***"there is no statistical difference against placebo concerning eventual malformations and outcomes and similar results were found when ginger was compared with the general population.*** Considering the toxicity in animal: ***"oral administration up to 2000 mg/kg was not associated with any mortalities and abnormalities in general conditions. For the reproductive and developmental toxicity the ginger dosages develop much higher toxicity in animal than usually dosages in humans."*** **Summary**: Ginger is a very ancient spice, used nowadays worldwide as a common condiment with also a long history of use as a medicinal drug (India…). There is no restriction of use and the rhizome is on the positive list of the FDA (G.R.A.S. Generally recognized as safe status). EMA has recognized two levels of therapeutic indications: "traditional use" and "well established use" and the assessment report confirmed this important point. Of course relevant guidelines such as EMEA/HMPC/107079/2007 (Guideline on the assessment of genotoxicity of Herbal substances / preparations) need to be met.	*This study is a non-randomised prospective study comparing ginger in general (cakes, capsules, tea, syrup, fresh etc) with a control group.*

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		This plant is of interest in the prevention of morning nausea and vomiting especially during pregnancy; a pathology starting at about 4-6 weeks of pregnancy and which disappear at 14-16 weeks. **All the conclusions of the report assessor are in favour of a use against specific nausea in pregnancy.** **Thus the conclusions of the monograph are surprising and not related with the expert conclusions.** **It seems that the mentions in the monograph concerning the** *"safety during pregnancy and lactation (which are) not been established"* **is too strict and that "** *in the absence of sufficient data, the use during pregnancy and lactation is not recommended***" is more a problem of precaution of health without any adverse serious clinical data than a real reflect of the hazard described in the scientific literature.**	