6 May 2010
EMA/HMPC/139995/2010
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Ilex paraguariensis* St. Hilaire, folium (EMA/HMPC/580539/2008)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Ilex paraguariensis* St. Hil., folium as released for public consultation on 16 July 2009 until 15 December 2009.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry - AESGP

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
AESGP	AESGP welcomes the preparation of the above-mentioned Community herbal monograph which may facilitate mutual recognition in Europe by providing harmonised assessment criteria for herbal medicinal products.	The comment is appreciated.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	AESGP	**Comments:** The powdered herbal substance available on the French market (Arkogélules Maté) as an encapsulated preparation. Encapsulated powdered mate folium was first marketed in France in 1988. A marketing authorisation has been granted to the product by the French authorities in December 1989. Herb powder for internal use has been cited in the German Commission E Monograph '*Mateblätter*' published in May 1988. Both the Mate dry extracts and the alcoholic tincture are described as preparations of mate in the literature [17] Additionally, the chemical profile of an extract produced with an hydroalcoholic extraction solvent (15% ethanol (m/m)) is equivalent to that of the Mate unroasted herbal drug and of the water infusion thereof which can be shown by experimental data from a company [18]. We therefore suggest including	Not endorsed. The tradition of medicinal use of powdered herbal substance was discussed in the MLWP. There is no additional information provided by AESGP. The tradition according to the provisions of Directive 2001/83/EC is not proven. Not endorsed. The reference to literature [17] is not suitable to prove a medicinal use for a period of thirty years because it is just a reference to the commission E monograph. This has already been taken into consideration during the preparation of the monograph and the AR. There is also no documentation of the tradition of the liquid extract

		these preparations as well. **Proposed change (if any):** Traditional use: i) Herbal substance ~~Not applicable.~~ Dried cut unroasted leaves and leaves stems ii) Herbal preparations Comminuted herbal substance **Powdered herbal substance** **Hydroalcoholic extracts or tinctures (max. 20% EtOH V/V) thereof.**	with 15% ethanol (m/m). Deviations from the period of thirty years could be assessed in national applications as well as data on comparability. According to the legislation, the HMPC could be involved on request of the national competent authorities.
3. Parmaceutical form	AESGP	**Proposed change (if any):** We propose the following modifications to be introduced: Traditional use: ~~Comminuted herbal substance~~ **Herbal substances and preparations in solid or liquid dosage forms or** as herbal tea for oral use.	Not endorsed. See above
4.1. Therapeutic indications		**Proposed change (if any):** We propose to add the following indication: **3) Traditional herbal medicinal product used as an adjuvant in weight loss programs** **Comments:** In France, Mate leaves have a traditional use as adjunctive treatment in weight loss programs [19, 20, 21]. The	Not endorsed. The use of preparations of mate in weight loss programs was discussed during drafting of the monograph and is reflected in the AR. The MLWP concluded that the tradition of use as

		traditional use of mate as an adjuvant in slimming diets was recognised by the French authorities in August 1986 [Bulletin official N° 86/20 bis, Spécialités pharmaceutiques à base de plantes] and later editions [Bulletin official N° 90/22 bis and Cahiers de l'Agence N° 3, September 1997]. The lipolytic action of mate folium was reported in the German Commission E Monograph '*Mateblätter*' (May 1988). Indeed, different textbooks dated from 1973 have described a lipolytic effect of mate folium [see 1 for a review of textbooks]. Mate folium has also been said repeatedly to dispel hunger as described in different textbooks from the middle of the 19th century [2-4]. It was reported as popularly used for loosing weight purposes in Porto Alegre, South Brazil [5]. Bisset [6] quoted that mate is praised as "the ideal slimming remedy which facilitates losing weight in a natural way and stills the distressing feelings of hunger and thirst". The plausibility of weight reduction efficacy is supported by different studies. Additive effects, from decreasing plasma levels of cholesterol and triglyceride in rats fed with a hypercholesterolemic diet [7], to activation of the metabolic process in rats rendered obese by a high-fat diet [8] and to suppressing of the appetite via prolong gastric emptying time in humans [9], have been described. One human study comparing the effects of twelve herbal preparations with claimed weight reduction activity demonstrated that mate folium preparation was the only one that decreases the respiratory quotient. This indicates a shift in metabolism whereby there is an increase in the burning of fat [1]. The chemical composition supports lipolytic activity of mate folium due to its caffeine content as its effect on energy	adjunctive treatment in weight loss programs is not convincing. It has to be differentiated between possible lipolytic effects by single components and adjuvant in weight loss programs. Studies on effects in weight loss programs are inconsistent. Results from recent studies were not significant or data were obtained in studies with combination products.

		metabolism has been thoroughly studied in humans, with the consistent finding of an increased thermogenesis related to the amount of caffeine ingested, as well as an increased lipolysis observed the days following caffeine consumption [10, 11]. Caffeine has been shown to cross the blood brain barrier and to increase the circulating concentration of catecholamine (epinephrine) in humans, which is known to increase thermogenesis [12] and lipolysis [13]. Additionally, the hypolipidemic effects could also be related to a fat absorption reduction due to the saponin content of mate folium as saponins are reported to interfere with cholesterol metabolism and to delay the intestinal absorption of dietary fat via inhibition of pancreatic lipase activity [14, 15]. Mate leaf saponins showed an inhibition of the passive diffusion of cholic acid in an *in vitro* system which could favour *in vivo* increased excretion of sterols [16].	
4.2 Posology and method of administration	AESGP	**Comments:** According to the above mentioned marketing authorisation for Arkogélules Maté, single dose of encapsulated powdered mate folium preparation corresponds to 220 mg with the following recommended daily dose: 220-440 mg 2 to 3 times daily (440-1320 mg per day). **Proposed change:** We propose: 1. to add to the Indications 1) to 3) Powdered herbal substance in hard capsules: • **Single dose: 220-440 mg** • **Daily dose: 440-1320 mg**	Not endorsed. See above

		2. to add to the indication 3) **Indication 3)** **Daily dose:** **Comminuted herbal substance as herbal tea: 3-6g corresponding to 3 times 1-2g of herbal substance per day**	
4.2 Posology and method of administration (duration of use)	AESGP	**Comments:** Concerning indication 1), and based on the recommendation of the Eleutherococci radix Community Monograph, it seems more appropriate to recommend to consult a doctor or a qualified health care practitioner if the symptoms persist longer than 2 weeks (instead of 1 week) during the use of the product. Concerning indication 3), one month of use corresponds to the classical duration of use of herbal preparations taken as adjuvant to hypocaloric diets to lose weight. **Proposed change:** Indication 1) **If symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.** Indication 3) **Duration of use should be restricted to one month**	Not endorsed. Due to the limited data and to guarantee a safe use of the traditional herbal medicinal products, it was decided to limit the duration of use as published in the monograph. Not endorsed. See above
4.4 Special warnings and precautions	AESGP	**Comments:** In line with the proposed introduction of an indication c) this section should read:	

for use		Traditional use Indications 1), 2) **and 3)** The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data. Not recommended before bedtime as it may cause sleep disturbances. Indication 2) If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	Not endorsed. See above.
4.6 Pregnancy and lactation	AESGP	**Comments:** We recommend the following rewording **Proposed changes:** Traditional use ~~There are no or limited data from use during pregnancy and lactation.~~ ~~The use should be avoided during 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**.	Not endorsed. The special wording in the section pregnancy and lactation was chosen to reflect the existing data which are limited but in summary do not support the use during pregnancy and lactation. The issue is addressed in the AR.
References		[1] Martinet A, Hostettmann K, Schutz Y. Thermogenic effects of commercially available plant preparations aimed at treating human obesity. Phytomedicine. 1999;6:231-8.	

		[2] Chevalier M. Maté. In: Rapports du jury international – Exposition universelle de 1867. Tome sixième. Groupe V. – Classes 41 à 43. Imprimerie administrative de Paul Dupont, Paris 1868, 529-530. [3] De Moussy M. Yerba-maté. In: Description géographique et statistique de la coopération Argentine. Tome premier. Librairie de Firmin Didot Frères, fils et C^{ie}, Paris 1860, 428-434. [4] Demersay A. III. Propriétés, action physiologique et usages du maté. In: Etude économique sur le maté ou thé du Paraguay. Extrait des mémoires de la société d'agriculture année 1868. Société impériale et centrale d'agriculture de France. Ve Bouchard-Huzard. Paris 1867, 23-30. [5] Dickel ML, Rates SM, Ritter MR. Plants popularly used for loosing weight purposes in Porto Alegre, South Brazil. J Ethnopharmacol. 2007; 109:60-71. [6] Bisset NG. Mate folium. In: Herbal drugs and phytopharmaceuticals – a handbook for practice on a scientific basis. Medpharm, Stuttgart 1994, 319-321. [7] Paganini Stein FL, Schmidt B, Furlong EB, Souza-Soares LA, Soares MC, Vaz MR, Muccillo Baisch AL. Vascular responses to extractable fractions of *Ilex paraguariensis* in rats fed standard and high-cholesterol diets. Biol Res Nurs. 2005; 7:146-56. [8] Pang J, Choi Y, Park T. *Ilex paraguariensis* extract ameliorates obesity induced by high-fat diet: potential role of AMPK in the visceral adipose tissue. Arch Biochem Biophys. 2008; 476:178-85. [9] Andersen T, Fogh J. Weight loss and delayed gastric emptying following a South American herbal preparation in	

		overweight patients. J Hum Nutr Diet. 2001; 14:243-50. [10] Bracco D, Ferrarra JM, Arnaud MJ, Jéquier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. Am J Physiol. 1995; 269:671-8. [11] Dulloo AG. Ephedrine, xanthines and prostaglandin-inhibitors: actions and interactions in the stimulation of thermogenesis. Int J Obes Relat Metab Disord. 1993; 17 (Suppl 1):S35-40. [12] Astrup A, Toubro S, Cannon S, Hein P, Breum L, Madsen J. Caffeine: a double-blind, placebo-controlled study of its thermogenic, metabolic, and cardiovascular effects in healthy volunteers. Am J Clin Nutr. 1990; 51:759-67. [13] Hetzler RK, Knowlton RG, Somani SM, Brown DD, Perkins RM. Effect of paraxanthine on FFA mobilization after intravenous caffeine administration in humans. J Appl Physiol. 1990; 68:44-7. [14] Hosttetmann K, Marston A. 1995. Saponins. University Press, Cambridge, New York, USA. [15] Han LK, Zheng YN, Xu BJ, Okuda H, Kimura Y. Saponins from platycodi radix ameliorate high fat diet-induced obesity in mice. J Nutr. 2002; 132:2241-5. [16] Ferreira F, Vasquez A, Güntner C, Moyna P. Inhibition of the passive diffusion of cholic acid by *Ilex paraguariensis* St. Hil. saponins. Phytother Res 1997; 11:79-81. [17] Blumenthal M, Goldberg A, Brinckmann J. Herbal Medicine. Expanded Commission E Monographs. Newton:	

		Integrative Medicine Communications, 2000. [18] Frutarom Switzerland Ltd, unpublished data. Available on request if required. [19] Bruneton J, 1995. Pharmacognosy, Phytochemistry, Medicinal plants. Paris: Lavoisier Publishing. [20] Ministère des Affaires Sociales et de la Solidarité de la France (1990). Avis aux Fabricants concernant les demandes d'autorisation de mise sur le marché de médicaments à base de Plantes, Fascicule spécial No 90/22 bis. [21] Bradley P, 2006. British Herbal Compendium, Vol. 2. British Herbal Medicine Association.	