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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Ilex paraguariensis* St. Hilaire, folium

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HMPC decision on review of monograph *Ilex paraguariensis* St. Hilaire, folium adopted on 06 May 2010.	15 January 2020
Call for scientific data (start and end date)	From 01/04/2020 to 30/06/2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	05 May 2021

Review of new data on *Ilex paraguariensis* St. Hilaire, folium

Periodic review (from 2010 to 2020)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

The EudraVigilance database was searched on 20/10/2020 using the keywords "*Ilex paraguariensis*", and "Mate"

☒ Scientific/Medical/Toxicological databases

Base; Embase; Pubmed; Biomedical Reference Collection; DynaMed (result of 31/08/2020: key words "*Ilex paraguariensis*", and "yerba mate"

☐ Other

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

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☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☒ Ph.Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

Other

☐

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☒	☐
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review 1496 new references not yet available during the first/previous assessment were identified. Filter used were "English language" and "peer-reviewed journals".

No references were provided by Interested Parties during the Call for data.

32 references were considered to be relevant for the assessment.

0 references justify a revision of the monograph.

A monograph on Mate folium (9.4/2678) was newly included in Ph. Eur. 9.4 (European Pharmacopoeia, 2018); it replaces the DAC monograph "Grüne Mateblätter" (green Mate leaf).

No revision is considered required because no new data/findings of relevance for the content of the monograph. Reference to the new pharmacopoeia monograph should be adapted in the HMPC monograph when there is a need to revise the monograph.

Scientific data

Clinical efficacy

Various studies have been published that investigate the influence of mate intake on various blood and body parameters.

da Veiga *et al*. (2018) and Conforti *et al*. (2012) explored the effects of yerba mate tea drinking (at least 1l per day) in postmenopausal women in observational studies (either as post-hoc analysis of a case-control study or as cross-sectional study). Both studies showed small positive effects, such as fewer diagnoses of dyslipidaemia, hypertension, and coronary disease or a higher bone mineral density (measured on lumbar spine and femoral neck).

Another study (Calixto *et al*. (2020)) investigated the impact of yerba mate consumption on the clinicopathological profile of women with breast cancer. According to the authors, the findings suggest that yerba mate consumption affects the blood antioxidants of breast cancer patients, and the caffeine present in this mixture may favour the development of tumour of good prognosis.

Several studies were performed in the field of obesity/metabolic diseases. Effects e.g. on diabetes related biomarkers, blood lipid concentrations, body fat mass, percent body fat and waist-hip ratio, lipid parameters, blood viscosity or antioxidative stress biomarkers (Sarriá *et al*., 2020a; Sarriá *et al*., 2020b; Balsan *et al.*,2019; Becker *et al*., 2019; Cahuê *et al*., 2019; Panza *et al*., 2019; Kim *et al*., 2015; Gambero & Ribeiro, 2015; Yu *et al*.,2015; Boaventura *et al*., 2013) were seen in the settings chosen, while other studies showed no effects on lipid profiles in special patient groups (Souza *et al*.,2017).

Gatto *et al*. (2015) described from a case-control study an inverse association between yerba mate consumption and Parkinson's disease. Sahebkar-Khorasani *et al*. (2019) reported about studies showing short-term evidence for suppressing appetite.

Assessor's comment:

No revision is considered required because medicinal products corresponding to the indications described in the above-mentioned clinical studies are not reported from the EU market. Therefore, the well-established use criteria are not fulfilled. In these studies, commercial samples of mate leaves or extracts were used which may not correspond to the herbal tea as described in the HMPC monograph on I. paraguariensis.

Clinical safety

Pegoraro *et al*. (2018) evaluated the association between the consumption of yerba mate and the presence of micronuclei in the oral mucosa that signs the extent of damage that an aggressor agent may cause in the oral cavity. Data collection included the collection of cells of the buccal mucosa and the application of a questionnaire on the consumption habits of 120 individuals. The results showed that there are no statistically significant differences regarding the presence of micronuclei between the periodic consumption of yerba mate and no consumption at all, as well as between daily consumption and periodic consumption. The authors concluded that consuming yerba mate does not represent a risk factor for the significant increase in the number of micronuclei in the oral mucosa.

Lopes *et al*. (2018) studied exposure to polycyclic aromatic hydrocarbons (PAHs) in mate drinkers over a wide range of mate consumption. 244 adults were recruited, who answered a questionnaire and collected a fasting spot urine specimen. Urinary concentrations of seven PAH metabolites were quantified and associations between self-reported recent mate consumption and urinary PAH metabolites were assessed by multivariate regression. Recent mate consumption showed a significant dose-response association with 6 of 7 PAH metabolites. The sum of the urinary concentrations of the phenanthrene metabolites was similar or higher among mate drinkers who did not smoke than among smokers who did not drink mate. The authors concluded that drinking mate is a source of exposure to potentially carcinogenic PAHs, consistent with the hypothesis that the PAH content of mate may contribute to the increased risk of esophageal squamous cell carcinoma (ESCC) in mate drinkers.

Lubin *et al*. (2014) examined whether drinking mate tea may increase the risk of ESCC and other cancers due to PAH and/or if thermal injury would be responsible for these effects. Two case-control studies were pooled: a 1988 to 2005 Uruguay study and a 1986 to 1992 multinational study in Argentina, Brazil, Paraguay, and Uruguay, including 1400 cases and 3229 controls. Odds ratios (ORs) for ESCC increased linearly with cumulative mate consumption and were unrelated to intensity, so greater daily consumption for shorter duration or lesser daily consumption for longer duration resulted in comparable ORs. The strength of association increased with higher mate temperatures.

Vieira *et al*. (2010) evaluated the presence of potentially pathogenic fungi in 8 brands of yerba mate commercially available in Southern Brazil. Because hot water is generally used to prepare yerba mate infusion, the effect of several temperatures on fungal growth was also investigated. All but 1 yerba mate brand showed substantial fungal growth. Some of these fungi were able to survive extreme variations in pH and temperature. The authors concluded that because of the potential for yerba mate to carry pathogenic fungi, immunocompromised patients might be at risk of acquiring invasive fungal diseases by drinking yerba mate infusion.

Rodriguez *et al*. (2019) described the case of a young man (21 years of age) with acute hepatitis secondary to the use of yerba mate. Roussel Uclaf Causality Assessment Model (RUCAM) score was 65.4. He had negative viral hepatitis markers including hepatitis A, B, C, E, cytomegalovirus, herpes simplex, adenovirus, and varicella zoster virus. He reported daily yerba mate tea during the four months he spent in Argentina, sometimes twice a day and symptoms began during the last two weeks he stayed there. He continued drinking the tea until the last day of his vacations, before coming back to the United States. All of his co-workers had drunk the same tea on a daily basis; however, no one else developed similar complaints. Hepatotoxic pattern was cholestatic liver, which correlates with a possible hepatic sinusoidal obstruction syndrome-like presentation. After two months, all numbers came back to normal levels.

Assessor's comment:

The studies do not contradict the existing AR. In addition, the new studies do not clarify which factors (e.g. PAH content, drinking temperature) contribute to the described adverse effects of mate tea consumption. Concerning the PAH content see existing AR (EMA/HMPC/580545/2008) and "Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/300551/2015).

Concerning the case of acute hepatitis, the patient had consumed a commercially available mate tea, which probably does not correspond to the herbal mate tea as described in the HMPC monograph. According to the author of this case report "it is also possible that some of these drinks might have the presence of adulterants that may be incorporated into the final product, either intentionally or unintentionally".

Eudravigilance data

In EudraVigilance database for the period up to October 2020 there was one spontaneous report (from 2014) of suspected adverse drug reaction associated with *I. paraguariensis*. A woman (32 years old) took three supplements (2 out of them for 2 months, Herba Mate for 7 days), all up to hospital admission. She was diagnosed with toxic hepatitis compatible with drug-induced acute toxic hepatitis. Started feeling nauseatic 4 days before admission then, experiencing loose and frequent stools on the day of admission. Dark urine last 7 days, which was seen to make Herba Mate less likely suspect.

Assessor's comment:

There are no new safety concerns from the case report in the Eudravigilance database up to October 2020.

PAHs in Mate

In several studies the PAH content of Mate samples was investigated.

Table 1: Examples for the determination of PAH content in yerba mate

PAH-content	**Content**	**Reference**
benzo(b)fluoranthene	0.02 - 0.09 µg/g	Nwankwo *et al*. (2019)
PAH4	194 - 1795 µg/kg	Tfouni *et al*. (2018)

PAH8 Benzo[a]pyrene	371.2 - 2438.8 ng/l in hot infusions 19.2 - 937.3 ng/l in cold infusions 37.0 - 373.9 ng/l in hot infusions 7.0 - 92.1 ng/l in cold infusions	Thea *et al*. (2016)
PAH4	200 - 800 ng/g in dry tea	Kowalski *et al*. (2015)
PAH16 PAH4	224.6 - 4449.5 µg/kg on dry mas 8.3 - 512.4 µg/kg on dry mass	Londoño *et al*. (2014)
PAH16	1600 - 2500 µg/kg	Schulz *et al*. (2014)
PAH20 Benzo[a]pyrene	621 - 1990 ng/g 5.11 - 21.0 ng/g	Golozar *et al*. (2012)

Oranuba *et al*. (2019) summarized 10 original articles that had measured PAHs in commercial dry samples of Mate leaves. Nearly all found very high mass fractions. Most studies found benzo[a]pyrene mass fractions to be over 25 ng/g, and some found levels up to 600 ng/g. It was pointed out, that carcinogenic PAHs are often hydrophobic, and may not readily transfer into infusions. Seven articles studied transfer rates and these rates varied from 1 to 50%, depending on the methods employed.

Assessor's comment:

The results will not change the content of the monograph. The quality of the mate-leaves used (e.g. pharmaceutical quality) has not been described. In the AR (EMA/HMPC/580545/2008) of I. paraguariensis it was already pointed out that against the background of the PAH formation due to special drying conditions yerba mate roasted leaves according to the DAC monograph M-065 are excluded from the HMPC monograph to reduce the occurrence of PAH in medicinal products. Also, the new Ph. Eur. monograph (European Pharmacopoeia, 2018) refers to the rapidly desiccated dried (yellowish-green to brownish-green) leaves of I. paraguariensis and excludes therefore the "roasted mate leaves" (brown colour). Furthermore, see "Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/300551/2015).

Non-clinical toxicology

Jang *et al*. (2018) investigated hepatoprotective effects of *Ilex paraguariensis* 70% ethanol extract (IPEE) against carbon tetrachloride-induced liver injury in an animal model. IPEE (200 and 400 mg/kg/day) were administered to rats for 7 days prior to a single dose of CCl_4. Organs were collected for biochemical, histological, and molecular study after 24 hours of CCl4 application. The gamma glutamyltransferase, alkaline phosphatase, alanine transaminase and aspartate transaminase in CCl_4-treated control were 9, 32, 401 and 168% increased as compared to non-treated control. The superoxide dismutase, glutathione and glutathione peroxidase levels in IPEE-pre-treated rats were similar to non-intoxicated control but were seriously affected in CCl_4-treated control. The IPEE pre-treatment reduced hepatic lesions and necrosis, and expressions of PPARa and CYP4A2 were recovered about 48% by 400 mg/kg/day of IPEE-pre-treatment. The extract appeared to be non-toxic in acute toxicity study.

Acute toxicity of yerba mate dried extract (YMDE) was investigated in Wistar rats (6/sex/group) from single dose of 2 g/kg body weight by intragastric administration and 14 days monitoring. Subchronic toxicity was investigated in Wistar rats, by intragastric administration (10/sex/group), and in New Zealand rabbits by oral administration (3/sex/group) of 2 g/kg body weight for 12 weeks. Toxicological parameters included clinical signs, body weight, water, and food consumption, haematological and serum parameters, and histopathological assessment. Acute YMDE administration showed no effects on survival, clinical observations, macroscopic examination of organs, body weight or food, and water consumption. Sub-chronic administration of YMDE did not change behaviour, body weight, and histopathological assessment of stomach, kidney, liver, and small gut. Moreover, most of biochemical and haematological parameters remained unchanged. It was concluded that the results of the preclinical toxicological investigation are indicative that the YMDE is well tolerated for both single and chronic administration (de Andrade *et al*., 2012).

The aim of the study from Feltrin *et al*. (2019) was to develop and to apply Caco-2 cells-based gene reporter assays to study *in-vitro* the potential occurrence of CYP3A4 and CYP2D6 gene expression modulation by extracts of selected medicinal plants. The extracts of *I. paraguariensis* significantly decreased CYP2D6 reporter fluorescence in Caco-2 cells-based gene reporter assays but had no influence on CYP3A.

Assessor's comment:

The studies on acute and subchronic toxicity and interactions have no influence on the monograph.

Non-clinical pharmacology

Many *in vitro* and *in vivo* studies examining potential health effects of yerba mate were published within the last decade. Similar to the clinical investigations, anti-obesity and anti-oxidative properties are in the centre of attention. In addition, single publications covering other aspects (e.g. antimicrobial activity, antiviral activity, anti-Alzheimer effects) were found.

Since such data will not have any influence on the monograph, the assessment of these studies has been waived.

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b) References that justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on *Ilex paraguariensis* St. Hilaire, folium by consensus.