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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Camellia sinensis* (L.) Kuntze, non fermentatum folium

Rapporteur(s)	C. Purdel
Peer-reviewer	I. Chinou

HMPC decision on review of monograph *Camellia sinensis* (L.) Kuntze, non fermentatum folium adopted on 12 November 2013	13 January 2021
Call for scientific data (start and end date)	From 01 February 2021 to 30 April 2021
Adoption by Committee on Herbal Medicinal Products (HMPC)	20 July 2022

Review of new data on *Camellia sinensis* (L.) Kuntze, non fermentatum folium

Periodic review (from 2011 to 2021)

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

- ☒ Scientific/Medical/Toxicological databases: PubMed was searched on 10 June 2021
- ☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

Regulatory practice

- ☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)
- ☒ New market overview (including pharmacovigilance actions taken in member states)
- ☐ Referral
- ☒ Ph. Eur. monograph
- ☐ Other

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☒ 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, 3068 new references not yet available during the first assessment were identified. Considering the significant number of new references, further filters were used such as: case reports, randomised control trials, systematic review, etc. During screening of the selected articles, supplementary selection criteria were used, such as the level of characterisation of the preparation or the therapeutic areas investigated in clinical trials.

33 references were considered relevant for the assessment.

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

Scientific data

Toxicological data

NTP study

NTP performed genotoxicity tests (*Salmonella typhimurium*, *Escherichia coli*, and mouse peripheral blood erythrocytes), 3-month toxicology studies in F344/NTac rats and B6C3F1/N mice and 2-year toxicology and carcinogenicity studies in Wistar Han rats and B6C3F1/N mice using oral gavage administration of a green tea extract (DER not declared; extraction solvent: ethanol:water; the extract contains 48.4% (w/w) epigallocatechin gallate (EGCG)).

Green tea extract was mutagenic in *S. typhimurium* (strains TA98 and TA100) when is tested with metabolic activation using hepatic microsomes from rat livers S9. No mutagenicity was observed in these strains without metabolic activation or in the *E. coli* strain WP2 *uvr*A/pKM101, with or without metabolic activation. *In vivo*, no increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male or female B6C3F1/N mice in the 3-month study.

Under the conditions of the 2-year gavage studies, there was no evidence of carcinogenic activity of green tea extract in male or female Wistar Han rats administered 100, 300, or 1,000 mg/kg. There was no evidence of carcinogenic activity of green tea extract in male or female B6C3F1/N mice administered 30, 100, or 300 mg/kg (NTP, 2016).

Assessor's comment: The used extract is not corresponding to any herbal preparation described in the EU herbal monograph on Camellia sinensis. Hence, this new data alone does not trigger a revision of the monograph.

Hepatotoxicity

Occurrence of hepatotoxicity with varying degrees of severity was reported in mice treated with the preparation described before (extraction solvent: ethanol:water; the extract contains 48.4% (w/w) EGCG). The severity of toxicity progressed in a dose-dependent manner, ranging from centrilobular hypertrophy without pathological lesions, mild elevation of liver enzymes, to severe hepatocellular necrosis and bile duct hyperplasia (NTP, 2016).

Assessor's comment: As the used extract is not corresponding to any herbal preparation described in the green tea monograph, given data are not considered relevant for the EU herbal monograph.

Clinical efficacy data

A significant number of articles (e.g. reviews, meta-analyses, clinical studies) have been published during the review period. Various reviews have been published that investigated the effects of green tea extracts or isolated compounds (EGCG) in reduction of body weight (e.g. Jurgens *et al.,* 2012; Rothenberg *et al.,* 2018; Vazquez *et al.,* 2017), alleviation of metabolic syndrome (e.g. Suliburska *et al., 2012*; Yang *et al.,* 2018), prevention of diabetes (e.g. Shanafelt, *et al.,* 2013; Nguyen *et al.,* 2012) and cardiovascular diseases (Bogdanski *et al.,* 2012; Hartley *et al.,* 2013).

Also, many systematic reviews and meta-analyses have been undertaken in recent years to examine the association between green tea consumption and cancer risk (e.g. Guo *et al.,* 2017; Ni *et al.,* 2017; Gianfredi *et al.,* 2018, Filippini *et al.,* 2020), but the results are inconclusive.

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 considered fulfilled. The extracts or the isolated metabolites used, are not covered by the EU herbal monograph on Camellia sinensis.

In accordance with the guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established (WEU) and traditional herbal medicinal products'

(EMA/HMPC/104613/2005 – Rev. 1), the assessment of new scientific data should also include an assessment if the products reported on the EU market by the NCAs in the market overview can be considered as similar to the product studied in new relevant studies found in the literature.

A preparation that is not included in the previous version of the EU herbal monograph now fulfil the criteria of 10 years of WEU: dry extract, purified (DER 45-56:1, extraction solvent: water) corresponding to 55-72% (-) epigallocatechin -3-O-gallate. This extract is known under the trade name 'Polyphenon E'.

Therefore, only clinical studies on 'Polyphenon E' have been considered relevant for assessment of clinical efficacy during this periodic review. Furthermore, clinical studies in therapeutic areas lacking 10 years of WEU in EU have been considered not relevant during this periodic review.

Regarding the 'Polyphenon E' and its cutaneous use in the treatment of external genital warts, 4 randomised, double-blind clinical studies were identified (Gross *et al.,* 2007; Tatti *et al.,* 2008; Tatti *et al.,* 2010; Stockfelth *et al.,* 2008). The trials investigated the clinical efficacy of two different formulations (containing 10% and 15% Polyphenon E) in the treatment of external genital warts for 12 or 16 weeks. According to the authors the preparation tested is effective in the treatment of external genital warts.

Reference	Study design	Test product, posology	Number of subjects	Outcomes	Comments on clinical relevance of results
Gross *et al.,* 2007	Randomised, double-blind, four-arm parallel-group, placebo-controlled study	Polyphenon E 10% cream, Polyphenon E 15% ointment or placebo Topical applied to all external genital warts 3 times a day 12 weeks	242 patients (125 men, 117 women)	The complete clearance of baseline warts	For 15% Polyphenon E ointment, statistically significant differences to placebo were achieved regarding the complete clearance of all baseline external genital warts (61.0% vs. 40.5% in males, 56.8% vs. 34.1% in females) For 10% Polyphenon E cream, 53.8% males and 39.5% females achieved the complete clearance. Recurrence rates 12 weeks after end of treatment were 10.6%, 11.8% and 10.3% for 15% ointment, 10% cream and placebo, respectively
Stockfelth *et al.,* 2008		Polyphenon E 10% ointment, Polyphenon E 15% ointment or placebo Topical applied to all external genital warts 3 times a day 16 weeks	503 immunocompetent patients	The complete clearance of baseline and new anogenital warts	About 53% of patients treated with Polyphenon E 15% ointment showed the complete clearance of all baseline and new anogenital warts, 51% for Polyphenon E 10% ointment, and 37% for vehicle. Women responded better than men, with about 60% of women and 45% of men in both active groups achieving the complete clearance of all warts. Time to complete clearance was comparable for both strengths of Polyphenon E ointment. About 78% of all patients treated with either Polyphenon E 15% or 10% ointment showed wart clearance rates of 50% or better. Less than 6% and 4% of patients in the Polyphenon E

Reference	Study design	Test product, posology	Number of subjects	Outcomes	Comments on clinical relevance of results
					15% and 10% ointment groups experienced wart recurrence during follow-up
Tatti *et al.,* 2008	Randomised, double-blind, vehicle-controlled trial	Polyphenon E ointment 15% or 10% or placebo 3 times daily for a maximum of 16 weeks or until complete clearance of all warts, followed by a 12-week treatment-free follow-up to assess recurrence	502 patients	The complete clearance of baseline and new warts	The complete clearance of all baseline and newly occurring warts was obtained in 57.2% and 56.3% of patients treated with Polyphenon E ointment 15% and 10%, respectively, compared with 33.7% for placebo (both $p<0.001$) During the follow-up, recurrence of any wart was observed in 6.5%, 8.3%, and 8.8% in the ointment 15% group, ointment 10% group, and placebo patients, respectively
Tatti *et al.,* 2010	2 randomised, double-blind, vehicle-controlled trials	Polyphenon E ointment 15% or 10% or placebo applied 3 times daily until complete clearance of all external genital warts or for a maximum of 16 weeks	986 patients	The complete clearance of all external genital warts	The complete clearance of all external genital warts was obtained in 53.6% (Polyphenon E ointment 10%) and 54.9% (Polyphenon E ointment 15%) of patients with Polyphenon E vs. vehicle (35.4%) ($p<0.001$). Statistically significant differences in clearance rates appeared after 6 weeks of active treatment. Time to complete clearance was shorter with active treatment and recurrence rates during the follow-up were low and similar across groups

Assessor's comment: The extracts used in these trials were characterised only by the trade name but not also by DER, nature and strength of the extraction solvent(s) or the content in epigallocatechin -3-O-gallate. Therefore, it is not demonstrated that these are comparable to the preparation that now fulfil the criteria of 10 years of WEU: dry extract, purified (DER 45-56:1, extraction solvent: water) corresponding to 55-72% (-) epigallocatechin -3-O-gallate.

In conclusion, these data have only limited value and cannot support the inclusion of a new preparation in the monograph.

Clinical safety data

In the sub-chapter '5.3. Adverse events and serious adverse events and deaths' of the first assessment report on green tea it is pointed out that the cases of hepatotoxicity reported in EU are correlated with high doses of green tea dried extracts consumed orally for therapeutic purposes other than the proposed indication in the HMPC monograph.

During the period covered by the review report numerous articles investigated the corelation between green tea consumption (especially for extracts) and the incidence of liver injury. The review report includes only the information connected with the preparations included in the EU herbal monograph so excludes the assessment of all extracts.

The European Food Safety Authority (EFSA) published a scientific opinion on the safety of green tea catechins and concluded that catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe. The rare cases of liver injury have been reported after consumption of green tea infusions most probably due to an idiosyncratic reaction (EFSA, 2018). EFSA noted that the number of human cases with hepatotoxicity associated with consumption of green tea infusions is extremely low compared to the large number of consumers of green tea infusions.

EFSA also declared that the intake of green tea extracts with doses $\geq$800 mg EGCG per day has been shown to induce a statistically significant increase of serum transaminases in treated subjects. At the same time, EFSA concluded that it was not possible to identify an EGCG dose from green tea extracts that could be considered safe.

Assessor's comment: Considering the concentrations of EGCG in green tea samples mentioned by EFSA (28.8 mg/g EGCG) the level of 800 mg EGCG per day is far exceeding the maximum daily intake of 316.8 mg EGCG resulting from the intake according to the maximum daily posology according to the EU herbal monograph. The value of 316.8 mg EGCG is comparable with the mean exposure from brewed green tea reported by EFSA in adults (321.21 mg EGCG).

EFSA assessment covered the cases reported up to 2018 and identified eight published case reports that suggested a possible association between the consumption of green tea infusions and liver injury. Only four cases (Rodhe *et al.,* 2011; Arzenton, 2012; Gallo *et la.,* 2013; Lugg *et al.,* 2015) were published after the EU herbal monograph was released and just 1 (Gallo *et al.,* 2013) referred to the ingestion of micronised herbal substance while the other cases referred to green tea infusions.

All the other cases identified in literature referred to green tea extracts

Publications	Product	Patient information and number of cases	Intake	Concomitant use	Observations	Comments	DILIN score for GTE (GT)	RUCAM score (calculated by DILIN)
Arzenton, 2012	Green tea infusion	62, F	2-3 cups green tea daily for 9 months equivalent to about 375 mg catechins per day, of which 270 is EGCG	None	Acute hepatitis Liver biopsy showed a "drug toxic damage", characterised by a hepatocellular confluent necrosis in zone 3 of hepatic acinus in perivenular area. After 4 months of stopping green tea infusions liver function tests were normalised and ferritin was reduced	Long latency, stopped for 2 months prior to presentation, took months to improve Contamination with PA was not checked Duration of use extremely high (9 months)	3*	7*
Gallo *et al.,* 2013	Japanese "matcha" green tea (micronised water-soluble powder)	42, F	Drinking tea (correspondent to 1.0 g per day of catechins) 10 days	Irbesartan, gestodene and 17α-ethinyl estradiol since several years	Autoimmune liver hepatitis Positive de-challenge when stopped	The patient carrying genetic variant of hepatic metabolism (HLA B*35:01 allele) developed an abnormal response to a combination of	3*	7*

Publications	Product	Patient information and number of cases	Intake	Concomitant use	Observations	Comments	DILIN score for GTE (GT)	RUCAM score (calculated by DILIN)
						agents (oral contraceptives + irbesartan + green tea) that normally would not be able to cause damage The quantity is significantly high compared with the EU herbal monograph		
Rohde 2011 – [Danish]	Green Tea infusion	55, F	4-6 cups (size not mentioned) of green tea per day 6 months	levothyroxine	Hepatic injury; increase liver function test results; liver transaminases were normal 2 weeks after discontinuation of the green tea infusion	Duration of use extremely high	3*	9*

Publications	Product	Patient information and number of cases	Intake	Concomitant use	Observations	Comments	DILIN score for GTE (GT)	RUCAM score (calculated by DILIN)
Lugg *et al.,* 2015	Green Tea infusion	16, F	Over 3 cups per day (dose unknown) 3 months	Amoxicillin	Nausea, jaundice, abdominal pain, acute hepatitis Time to recovery: 60 days	Long duration of use Contamination with PA was not checked	3	6

*The score according to Oketch-Rabah HA *et al.,* 2020DILIN scale: 1 = definite; 2 = highly likely; 3 = probable; 4 = possible; 5 = unlikely; 6 = insufficient data; RUCAM scale: > 8 = highly probable; 6-8 = probable; 1-2 = unlikely; 0 or < 0 = excludes

Assessor comments: The medicinal use of Camelia sinensis *as herbal infusion according to the posology and method of administration defined in EU herbal monograph (not longer than 1 week) cannot be associated with the published case reports. The published reports mentioned a significantly higher duration of use (up to 9 months) and higher posology (up to 3 L of infusion. Also, in one case it is associated with a genetic variant of hepatic metabolism (HLA B*35:01 allele) that induced an abnormal response.*

There are several clinical studies that investigated the association between hepatotoxicity of green tea extracts, but just a few referred specifically to infusions (Basu *et al.,* 2011; Toolsee *et al.,* 2013; Henning *et al.,* 2015). These studies included healthy subjects or diabetic or cancer patients. The duration was from 14 days to 8 weeks and the daily intake of EGCG was up to 704 mg. No elevation of serum transaminases was reported in the studies with green tea infusions. There are no published data on powder herbal substance. These results confirm the potential safety in use of the green tea infusions.

Eudravigilance

EudraVigilance was searched by the Pharmacovigilance Department of NAMDMR for adverse reactions on 25 March 2021, using the keywords "green tea" and "*Camellia sinensis*"; cases related to any green tea extracts with cutaneous use indication were excluded.

Nine ICSRs reports were found for the reference period; reaction list: hepatitis, insomnia, nausea; the causality between exposure to green tea and adverse reactions reported was not confirmed.

Assessor's comment: These data do not trigger a revision of the monograph.

Interactions

Interaction with nadolol

In healthy volunteers, repeated intake of green tea (700 ml per day, containing approximately 320 mg EGCG) for 14 days resulted in a pronounced reduction in plasma concentrations of nadolol (-85% in the area under the blood concentration–time curve (AUC_{0-48}), without altering renal clearance of nadolol. Moreover, green tea significantly inhibited OATP1A2-mediated nadolol uptake (IC_{50}=1.36%). The authors suggest that green tea reduces plasma concentrations of nadolol possibly in part by inhibition of OATP1A2-mediated uptake of nadolol in the intestine (Misaka *et al.,* 2014).

The same researchers investigated the effect also after a single concomitant administration of 30 mg nadolol with 150 mL of brewed green tea (3 g tea/100 ml hot water). Also, in this study, green tea substantially decreased plasma concentrations of nadolol. Moreover, the reduction in nadolol bioavailability could persist for at least 1 hour after drinking a cup of green tea (Misaka *et al.,* 2020).

Abe *et al.,* investigated on healthy volunteers the effect of co-administration of nadolol with EGCG-concentrated green tea extract (GTE). The administered doses of EGCG in low-dose GTE corresponds to 48.7 mg, whereas in high dose GTE was estimated to be 146.6 mg. A single co-administration of EGCG-concentrated GTE decreased significantly the plasma concentrations of nadolol in healthy volunteers by approximately 30% (low dose) to 40% (high dose). GTE also reduced the urinary excretion of nadolol without changing its $t_{1/2}$ and renal clearance (Abe *et al.,* 2018).

Assessor's comment: The interaction between green tea infusion and nadolol is demonstrated after single or repeated intake of green tea infusion. For a single dose administered, the amount of herbal substance used to obtain the infusion (4.5 g green tea) is double in comparison with the highest single dose mentioned in the EU herbal monograph (2.2 g). For repeated dose, the amount of infusion (700 ml) and duration of use (2 weeks) are significantly higher than the posology and duration of use

stated in the EU herbal monograph. The results obtained with EGCG-concentrated green tea extract are not relevant for the revision as this preparation is not included in the monograph.

Other interactions

Interactions between EGCG concentrated green tea extract or isolated EGCG with other drugs such as lisinopril (Misaka *et al.,* 2021) or rosuvastatin (Kim *et al.,* 2017) were reported on healthy volunteers. As these preparations or isolated compounds are not included in the EU herbal monograph, these data will not trigger the revision of the monograph.

Regulatory practice

A preparation that is not included in the previous version of the monograph now fulfil the criteria of 10 years of WEU: dry extract, purified (DER 45-56:1, extraction solvent: water) corresponding to 55- 72% (-) epigallocatechin -3-O-gallate. This extract is on the EU market since 31 August 2009, authorised as an ointment (1 g ointment contains 100 mg dry extract) with the following indication: cutaneous treatment of external genital and perianal warts (condylomata acuminata) in immunocompetent patients from the age of 18 years.

Nevertheless, considering the main shortcomings of the clinical efficacy data (no DER, extraction solvent not declared), the inclusion of this preparation in the monograph is not supported by the published data.

A monograph on Green tea (ref.: 2668) was newly included in Ph. Eur. (European Pharmacopoeia, 2018). The content is expressed in caffeine (minimum 1.5%) and total catechins (minimum 8.0%, as (-) epigallocatechin -3-O-gallate). In the French pharmacopoeia (the quality reference declared in the EU herbal monograph) the content was expressed only in caffeine with another limit (minimum 2.0%).

Assessor's comment: No revision is considered required because there are no new data/findings of urgent relevance for the content of the monograph. Reference to the new pharmacopoeia monograph should be adapted in the EU herbal monograph and supporting documents when there is a need to revise the EU herbal monograph.

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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 *Camellia sinensis* (L.) Kuntze, non fermentatum folium, by consensus.