EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Paullinia cupana* Kunth (syn. *Paullinia sorbilis* Mart.), semen

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HMPC decision on review of monograph *Paullinia cupana* Kunth (syn. *Paullinia sorbilis* Mart.), semen adopted on 15 January 2013	13 January 2021
Call for scientific data (start and end date)	From 01 April 2021 to 30 June 2021
Discussion in Committee on Herbal Medicinal Products (HMPC)	November 2021 March 2022 May 2022 September 2022 November 2022
Adoption by Committee on Herbal Medicinal Products (HMPC)	23 November 2022

Review of new data

Periodic review (from 2012 to 2022)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

Scopus, PubMed, MEDLINE, HEAL-Link. Libraries: National and Kapodistrian University of Athens (NKUA), Laboratory of Pharmacognosy and Chemistry of Natural Products of NKUA.

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2012-February 2022. Keywords: *Paullinia cupana*, Guarana, Guarana seeds, *Paullinia cupana* seeds

☒ Pharmacovigilance databases

☒ data from EudraVigilance - May 2022

☒ from other sources (e.g. data from VigiBase, national databases - May 2022)

☐ Other

Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

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

☐ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ 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

Availability of new information that could trigger a revision of the monograph

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☒	☐
New clinical safety data that could trigger a revision 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 that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☒	☐
Other scientific data that could trigger a revision 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	☐	☒
New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☒	☐

Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☐	☒

Summary of new references

During the review, 112 new references not yet available during the first/previous assessment were identified. Out of these new references, 57 references were considered to be relevant for the monograph and 6 references were further discussed as they could potentially trigger revision of the monograph.

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

The majority of new references referred to phytochemical studies (mostly quantitative and qualitative analyses on caffeine content) as well as the uses of seeds as food supplement.

There were found some references with clinical studies on healthy subjects (food supplements area) and patients. Moreover, several references referred to known pre-clinical pharmacological activities (antioxidative, antimicrobial, anti-aging, *etc*).

Assessment of new data

New scientific data that could trigger a revision of the monograph

Clinical safety data

VigiLyze / Eudravigilance

Conjunctivitis (6 cases) in co-administration with medicine (dupilumab), for which the side effect conjunctivitis was reported; therefore it can be concluded that the use of *Paullinia cupana* had no causal relation with this side effect.

Palpitations (6 cases); the causality between exposure *Paullinia cupana* seeds and adverse reactions reported could be potentially referred to the caffeine content of the plant.

Assessor's comment:

The plausibility of provoked tachycardia by seeds of Paullinia cupana is already described in the assessment report and led to a contraindication for patients with cardiovascular disorders such as hypertension and arrhythmias. There are no new safety concerns from the case report in the Eudravigilance database up to May 2022.

Possible pharmacokinetic interaction with other medicinal products

The study of Rodrigues *et al.* (2012) has aimed to assess the potential herb-drug interaction among a standardised (certified) guarana extract and amiodarone (narrow therapeutic index drug) *in vivo* in rats. In a first pharmacokinetic study rats were simultaneously co-administered with a single dose of *Paullinia cupana* (821 mg/kg, p.o.) and amiodarone (50 mg/kg, p.o.), and in a second study rats were pre-treated during 14 days with *Paullinia cupana* (821 mg/kg per day, p.o.) receiving amiodarone (50 mg/kg, p.o.) on the 15th day. Rats of the control groups received the corresponding

volume of vehicle. Blood samples were collected at several time points after amiodarone dosing, and several tissues were harvested at the end of the experiments (24 h after dose). Plasma and tissue concentrations of amiodarone and its major metabolite (mono-N-desethylamiodarone) were measured and analysed. A significant reduction in the peak plasma concentration (73.2%) and in the extent of systemic exposure (57.8%) to amiodarone was found in rats simultaneously treated with *Paullinia cupana* and amiodarone; a decrease in tissue concentrations was also observed, showing an herb-drug interaction between *Paullinia* extract and amiodarone, with determined decrease on amiodarone bioavailability in rats.

Assessor's comment:

Rodrigues et al. (2012) observed a decrease in plasma and tissue concentrations of amiodarone in concomitant use with Paullinia cupana extract and determined a decrease on amiodarone bioavailability in rats. The single dose and pre-treatment was made with 821 mg/kg, p.o. of guarana powder (approximately 3 times the daily dosage described in the monograph taking into account the human equivalent dose and a body weight of 50 kg for a human subject). Although this could indicate a possible interaction potential due to the small factor, it will not lead to a change in the monograph, as only clinically observed interactions are to be included there.

Clinical studies

Unpurified *Paullinia cupana* dry extract showed encouraging results for chemotherapy-induced fatigue in previous studies. Two randomised, double-blind studies with a standardised dry purified *Paullinia cupana* extract (named PC-18) were performed. For both studies, recruited early breast cancer patients who had an increase in their fatigue scores after their first cycle of adjuvant chemotherapy. The first study compared an oral dose of 37.5 mg of PC-18 twice daily with placebo. The second study examined PC-18 at either 7.5 or 12.5 mg orally twice daily versus placebo. In both studies, PC-18 was not superior to placebo as assessed by both Chalder and Brief Fatigue Inventory (BFI) questionnaires, probably reflecting unexpectedly good placebo antifatigue activity. Since all capsules in both studies contained about 100 mg of magnesium silicate as an excipient, retrospectively evaluated frozen serum samples from the second study and found a significant increase in magnesium levels after patients received placebo. By multivariate analysis, higher pre-randomisation magnesium levels and higher BFI scores together with the use of a 12.5 mg dose of PC-18 all correlated significantly with higher posttreatment BFI scores. They have been observed no significant toxicities in any of the trials (Sette *et al.,* 2017).

In one very recent reference by de Araujo *et al*. (2021), a systematic review with a meta-analysis to assess evidence about the use of guarana fruit to manage fatigue in cancer patients was carried-out. All data collected and reviewed in this publication were extracted from Embase, Scopus, MEDLINE, CENTRAL, and CINAHL databases, clinical studies with patients who presented cancer-related fatigue as a primary outcome and who used guarana as a dietary supplement were included. The risk of bias in randomised clinical trials was analysed according to the Cochrane recommendations. A total of 383 studies were found, of which seven with a total of 427 cancer patients were included in the review. The instruments used to analyse fatigue were the BFI, the Chalder Fatigue Scale, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), and the Piper Scale. Meta-analysis was conducted for three studies about breast cancer, which presented sufficient data (already existing data in the assessment report of the monograph). The use of guarana did not reduce cancer-related fatigue compared with placebo groups (mean of -0.02 [95% CI -1.54, 1.50]; p=0.98) and the quality of evidence according to GRADE was very low. The results of this review showed that the use of guarana was not superior to the placebo groups.

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 and no efficacy could be shown in the indication. Therefore, the well-established use criteria are not fulfilled.

Clinical study in healthy subjects

Guarana seed extracts are popular worldwide for their stimulant, cognitive and behavioural effects. In the present study, in order to assess the effects on psychological well-being, anxiety and mood of a commercially available guarana preparation taken regularly over several days according to the labelled dosages and instructions, 27 healthy volunteers were enrolled in a prospective, randomised, single-blind, placebo-controlled, crossover study. Guarana 1050 mg daily after breakfast or placebo were given for 5 consecutive days. Assessment was performed one day after the last intake and included the psychological well-being (PWB) scales, the self-rating anxiety state scale (SAS), and the Bond-Lader mood scales. There were no significant differences between guarana and placebo in any of the 6 areas of PWB, in SAS, as well as in any of the 16 mood scales (Silvestrini *et al.,* 2013).

Assessor's comment:

In healthy subjects, a 5-day treatment with a commercial preparation of guarana used according to labelled instructions provided no evidence for any major effects on psychological well-being, anxiety and mood.

New regulatory practice that could trigger a revision of the monograph

A monograph on *Paullinia cupana* Kunth (syn. *Paullinia sorbilis* Mart.), seed was newly included in Ph. Eur. (04/2018:2669); it replaces the French Pharmacopoeia's monograph (Pharmacopée Française 'Guarana (graine de) - *Paullinia sorbilis* semen' 1997).

There are no new data/findings of relevance for the content of the monograph.

Reference to the new pharmacopoeial monograph should be adapted in the EU herbal monograph when there is a need to revise the monograph.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

New information not considered to trigger a revision at present but that could be relevant for the next review

Samples of toasted guarana seeds of different brands of guarana powder produced in different parts of Brazil were analysed, aiming to identify and quantify 16 PAHs. The samples were analysed by high-performance liquid chromatography equipped with fluorescence and UV–Vis detectors. Naphthalene was identified and quantified in the guarana samples (0.13 and 0.78 μg kg^{-1}) and both naphthalene and phenanthrene were found in two commercial guarana powder samples (0.36–1.54 and 0.03–0.06 μg kg^{-1}, respectively) (Veiga *et al.,* 2014).

Assessor's comment:

The quality of the guarana seed used (e.g. pharmaceutical quality) has not been described. Furthermore, see "Reflection paper on Polycyclic Aromatic Hydrocarbons in herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/300551/2015).

References

de Araujo DP, Pereira PTVT, Fontes AJC, Marques KDS, de Moraes ÉB, Guerra RNM, *et al.* The use of guarana (*Paullinia cupana*) as a dietary supplement for fatigue in cancer patients: a systematic review with a meta-analysis. *Supportive Care Cancer* 2021, 29(12):7171-7182, in press, doi 10.1007/s00520-021-06242-5

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Rodrigues M, Alves G, Lourenço N, Falcão A. Herb-drug interaction of *Paullinia cupana* (Guarana) seed extract on the pharmacokinetics of amiodarone in rats. *Evidence-Based Complementary and Alternative Medicine* 2012, 428560, in press, doi 10.1155/2012/428560

Sette CVM, Ribas de Alcântara BB, Schoueri JHM, Cruz FM, Cubero DIG, Pianowski LF *et al.* Purified dry *Paullinia cupana* (PC-18) extract for chemotherapy-induced fatigue: results of two double-blind randomized clinical trials. *Journal of Dietary Supplements* 2018, 15(5):673-683, in press, doi 10.1080/19390211.2017.1384781

Silvestrini GI, Marino F, Cosentino M. Effects of a commercial product containing guarana on psychological well-being, anxiety and mood: a single-blind, placebo-controlled study in healthy subjects. *Journal of Negative Results in Biomedicine* 2013, 12:1, in press, doi 10.1186/1477-5751-12-9

Veiga LL, Amorim H, Moraes J, Silva MC, Raices RS, Quiterio SL. Quantification of polycyclic aromatic hydrocarbons in toasted guaraná (*Paullinia cupana*) by high-performance liquid chromatography with a fluorescence detector. *Food Chemistry* 2014, 152:612-618, in press, doi 10.1016/j.foodchem.2013.11.154

Rapporteur's proposal on revision

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

☐ Revision likely to have an impact on the corresponding list entry (if applicable)

☒ 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