EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 March 2017
EMA/HMPC/326583/2017
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on draft public statement on *Piper methysticum* G. Forst., rhizoma (EMA/HMPC/450588/2016)

Table 1: Organisations and/or individuals that commented on the draft public statement on *Piper methysticum* G. Forst., rhizoma as released for public consultation on 15 December 2016 until 15 March 2017.

	Organisations and/or individuals
1	Association for Natural medicine in Europe e.V. (ANME)
2	German Pharmaceutical Industry Association (BPI – Bundesverband der Pharmazeutischen Industrie)
3	Herbresearch Germany
4	Zentralverband der Ärzte für Naturheilverfahren e.V. (ZAEN)*

* Note: ZAEN submitted comments concerning only the draft Assessment Report

Table 2: Comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
ANME	In a separate statement concerning the Draft Assessment Report on Kava we delivered details demonstrating that the assessment report cannot be considered "comprehensive": A lot of literature has not been taken into account, and the assessment report is based on partly questionable, partly wrong and partly incorrect information. We specifically delivered information on the composition of the kava extracts as derived from available sources, on the question of liver toxicity and carcinogenicity, and on the interpretation of the clinical results using unsuitable criteria: the argumentation in the assessment report is clearly based on another indication than that used by the kava extract preparation used for the treatment of anxiety according to the monograph of the German Commission E. All these shortcomings and errors would not allow drawing the definite conclusion for not recommending the creation of an HMPC monograph on kava. As long as there is no assessment report giving an appropriate presentation of the data on kava, this conclusion is clearly premature. We recommend postponing the publication of the public statement until an real assessment report is available, preferably one more based on facts than on assumptions.	Partially endorsed All comments related to the Assessment Report have been taken into consideration and appropriately addressed in the version revised after public consultation. Regarding liver toxicity and carcinogenicity- please see above For the assessment of clinical trials, the use of current guidelines is the accepted practice for HMPC (see other monographs as *Crategus spp. folium cum flore, Serenoa repens fructus).* HMPC assessed the clinical trials on kava according to current European guidelines concerning the clinical investigation of medicinal products indicated for anxiety disorders (CPMP/EWP/4284/02; CHMP/EWP/3635 and CHMP/EWP/4280/02). These guidelines are developed for medicinal products intended for the treatment of anxiety disorder, independent of the class of product under investigation. HMPC maintains its negative opinion regarding the possibility to create a monograph.

Interested party	Comment and Rationale	Outcome
BPI	The literature cited with the assessment appears incomplete. There are much more studies on pharmacology and even clinical use, studies that add to the overall conclusion on efficacy and safety. Especially the additional information on (the lack of) adverse effects including adverse liver effects would have been highly important for the overall conclusions. We recommend that the clinical studies performed with D,L-kavain be at least presented as supportive material. They provide additional confirmation that the kavalactones are the fraction of kava constituents predominantly responsible for the clinical efficacy.	Partially endorsed All the references provided by the interested parties were investigated. Nevertheless, the revised list of references is divided in two parts: first, the articles found to be relevant for assessment report and a second part with the references assessed but not cited (considered not relevant). HMPC agreed that the studies on synthetic (racemic) kavain should not be included in the assessment because have a limited relevance and cannot be extrapolated to the natural L-kavain.
BPI	The major argument for negatively assessing clinical trials with kava preparations was the study duration. It seems that the definition of a minimum study duration as well as further criteria such as a follow-up phase was derived from a therapeutic guideline on the treatment of generalised anxiety published in 2005 – well after the performance of most kava studies. The guideline was meant to be guidance for the planning of studies for the treatment of long-standing generalized anxiety, but was specifically meant for chronic disorders and for the use of paroxetine or venlafaxine. This guideline has no importance for kava: the indication is different and the mode of action differs between kava and antidepressants. Consequently, the definitions of this guideline cannot simply be transferred to kava and the assessment of the clinical trials.	Not endorsed. Please see above.
BPI	Further arguments used to negatively assess clinical studies were the lack of an	Not endorsed.

Interested party	Comment and Rationale	Outcome
	indication of a drug extract ratio and the definition of a daily kavalactone dose instead of an extract dose. The DER was, however, found in some cases. In addition, the reference to the kavalactone dose completely neglects how kava preparations are dosed. Kava has a fixed upper dose of kavalactones, thus the presentation in milligram daily kavalactones corresponds to the regulatory definition.	Not only DER but also the extraction solvent was missing from those studies. The daily dose was expressed in kavalactones dose, because these preparations, since the 80's are called "standardised extracts". It seems that the term "standardised" was used a long time before the actual "standardization" was defined and included in Ph.Eur. According to the published literature, the methods used for the "standardization"(assay) varied during the time (from TLC, IR spectroscopy to HPLC assay). The correspondence between results obtained with different methods was never declared and is difficult to be assessed. Based on the existing clinical data, HMPC considered that the efficacy is not demonstrated and these are not standardised extracts.
BPI	In the overall conclusions with the risk-benefit assessment (page 85), the assessor states "Repeated dose studies and carcinogenicity studies provided sufficient evidence in experimental animals for the carcinogenicity of one kava preparation". The emphasis here is "on one" preparation: this preparation is not disclosed in detail by the assessor, although the information is part of the documentation of the NTP report. The composition of the kava extract is highly unusual and favours the lipophilic fractions. The product tested was "Kaviar 30", an extract manufactured with supercritical CO2. This is absolutely not comparable with European ethanolic extracts are currently re-instated into their	Not endorsed. It was clearly stated that the NTP findings are attributed only to the preparation used in the carcinogenicity study. The certificate of analysis provided by NTP is not including data regarding the nature of the extraction solvent used, therefore the assumption that is a supercritical carbon dioxide extract has no justification.

Interested party	Comment and Rationale	Outcome
	marketing authorisations in Germany after the conclusion of the German graduated plan procedure.	Because the phyto-chemical comparability with other preparations is not demonstrated, the results were not extrapolated to other preparations.

Interested party	Comment and Rationale	Outcome
Herbresearch	Specific comments are submitted to the Draft Assessment Report (EMA/HMPC/450589/2016), on which the draft Public Statement is based. The literature search mentioned in the public statement was neither complete nor comprehensive, and the conclusions drawn of safety and efficacy of kava are not or not sufficiently supported by the available data. Correspondingly, we recommend that a conclusion for the public statement is only drawn once the known facts on kava have been properly assessed.	Partially endorsed All comments related to the Assessment Report have been taken into consideration and appropriately addressed in the version revised after public consultation. All the references provided by the interested parties were investigated. Nevertheless, the revised list of references is divided in two parts: first, the articles found to be relevant for assessment report and a second part with the references consulted but not cited (considered not relevant).
Herbresearch	The concerns about carcinogenicity and liver toxicity are addressed in detail in our comments on the draft assessment report. These concerns cannot be used as an argument for the rejection of the creation of an herbal monograph.	Not endorsed. a) Carcinogenicity studies provided sufficient evidence in experimental animals for the carcinogenicity of one kava preparation. In male mice there is a significant and dose-depending increase of rare hepatoblastoma

Interested party	Comment and Rationale	Outcome
		(0/50, 4/50, 9/50, 12/50). The corn oil was used as vehicle and only by incidence there was no hepatoblastoma in the control group (0/50); also in the historical controls this rare tumor varies between 1-4/50. So, even referring to historical controls the increase of hepatoblastoma would still be dose-depending. All the other liver tumors were also seen in vehicle control group and historical controls. Not only the type of tumor but also the target organ (liver) is also important. In humans the target organ seems to be the liver, which is in compliance with the findings of NTP. The relevance of such findings for humans cannot be excluded, especially if the study is mainly seen as evidence for such neoplastic mechanisms in the target organ. b) An important signal of herbal induced liver injury (HILI) is derived from spontaneous case reports. Up to July 2002, WHO identified worldwide 93 cases of suspected hepatotoxicity associated with the use of different kava preparations, including cases of liver failure resulting in liver transplants and deaths.The causality assessment performed by WHO using its scale, revealed that 61 cases were associated with the use of different kava preparations (8 cases were coded having a "probable" causality and 53 as

Interested party	Comment and Rationale	Outcome
		"possible"). Also in the UK, the Committee on Safety of Medicines Expert Working Group investigated in 2002 and 2005 the safety signals (in total 110 cases of adverse liver reactions of which 9 cases with a fatal outcome) and determined that kava was associated with an unacceptable risk of hepatotoxicity. These cases led to the withdrawal of the marketed products in some Member States due to safety concerns. After 2002, a few new case reports have been published, but in all cases RUCAM scores indicated that the liver injury is associated with ingestion of different kava preparations. Even excluding two cases (that involved unknown preparation and a combination), still there are new cases where the causality was demonstrated (RUCAM scores: + 5, + 6 and +10). The small number of new case reports that did not involved EU preparations could be correlated with the measurements took by different EU-Member states, that revoked the authorisations for kava products. HMPC maintains its negative opinion regarding the possibility to create a monograph and no further

Interested party	Comment and Rationale	Outcome
		changes with regard to the benefit-risk assessment were made in the assessment report.