28 January 2015
EMA/HMPC/586885/2014
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Ginkgo biloba* L., folium (EMA/HMPC/321097/2012)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Ginkgo biloba* L., folium as released for public consultation on 15 February 2014 until 15 June 2014

	Organisations and/or individuals
1	ARKOPHARMA Laboratories, France
2	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
3	Ipsen Pharma, France
4	Midas Pharma GmbH, Germany
5	Dr. Willmar Schwabe GmbH & Co. KG, Germany
6	Weleda S.A., France

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
IPSEN PHARMA	**2. Qualitative and quantitative composition** We propose to : - *Refer to the Ph.Eur. monograph to characterise the Well-established use Herbal preparations (see rationale below)* We are not in favour of proposing powdered herbal substance as traditional use (*see rationale below)*	Endorsed. Not endorsed. (see below)
IPSEN PHARMA	**4.1 Therapeutic indications** We propose to add the following Well-established use indications: - *Adjunctive treatment of vertigo of vestibular origin in addition to vestibular rehabilitation (see rationale below)* - *Symptomatic treatment of tinnitus (see rationale below)* -	Not endorsed. (see below)
IPSEN PHARMA	**4.4. Special warnings and precautions for use** We propose to delete the following from Well-established use "special warnings and precautions for indication": *In patients with a pathologically increased bleeding tendency (haemorrhagic diathesis) and concomitant anticoagulant and antiplatelet treatment, the medicinal product should only be used after consultation with a doctor.* *Preparations containing Ginkgo might increase susceptibility to bleeding, the medicinal product should be discontinued as a precaution 3 to 4 days prior to surgery (see rationale below)*	Not endorsed. (see below)
IPSEN PHARMA	**4.5. Interactions with other medicinal products and other forms of interaction** We propose to delete the following from Well-established use "Interactions with other medicinal products and other forms of interaction" *"If the medicinal product is taken concomitantly with anticoagulants (e.g. phenprocoumon and warfarin) or antiplatelet drugs (e.g. clopidogrel, acetylsalicylic acid), their effect may be influenced.* *Available studies with warfarin do not indicate that there is an interaction between warfarin and G. biloba products, but adequate monitoring is advised when starting, when*	Not endorsed. (see below)

Interested party	Comment and Rationale	Outcome
	changing G. biloba dose, when ending G. biloba intake or if changing product. *(see rationale below)*	
IPSEN PHARMA	**4.8. Undesirable effects** We propose to delete the following from Well-established use "Undesirable effects" *"Blood and lymphatic system disorders* *Bleeding of individual organs have been reported (eye, nose, cerebral and gastrointestinal haemorrhage). The frequencies are not known."* *(see rationale below)*	Not endorsed. (see below)
Midas Pharma GmbH	Midas Pharma GmbH welcomes the draft Community herbal monograph on *Ginkgo biloba* L., folium accompanied with companion documents (draft assessment report and draft reference list), prepared by the Committee on Herbal Medicinal Products (HMPC), after *Ginkgo biloba* had been added to the inventory and priority list, respectively in 2007. The contents of this draft monograph are relatively low as compared to many other monographs on herbal preparations. A large number of general, preclinical and clinical publications remain unaddressed in the draft Assessment Report. Even the consolidated pharmacopoeia of the American Herbal Society (2003) was not considered. Despite the mode of action is not fully understood, a row of mainly preclinical investigations highlight interactions of *Ginkgo biloba* with neuronal network and neuronal transmitter systems. Section 3.3.1. of the assessment report refers to the anti-oxidative properties of *Ginkgo biloba* and the improvement of blood flow and microcirculation. Interactions and influences on neuronal network and neuronal plasticity are not considered. Some selected publications on the mode of action are listed in the attachment. Relevant published and unpublished studies on mutagenicity and genotoxicity are not considered. Instead a completely irrelevant study is displayed in extensio. Please find detailed comments below.	The Assessment Report is summarising the data which contribute to establishing a harmonised view in a European Union Monograph. It is mentioned in the disclaimer of the draft assessment report supporting the public consultation on the monograph that the focus is not to comment on the assessment report. If suggestions for changes of the monographs are justified and substantiated with references, the suggestions are discussed and if finally endorsed the relevant documents will be amended. With respect to the existing literature it is not the objective to include all publications. If appropriate specific references are added. (see below)
Dr. Willmar	We welcome the HMPC's conclusion that dry extract from Ginkgo biloba (DER 35-67:1),	

Interested party	Comment and Rationale	Outcome
Schwabe GmbH & Co. KG (Schwabe)	extraction solvent: acetone 60% m/m, fulfils the criteria of the well-established use status for the indication "Herbal medicinal product for the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia." This indication covers the conditions in which the clinical efficacy has been demonstrated most robustly. We appreciate the wording of the indication as it can be classified under the comprehensive diagnostic category Neurocognitive Disorder (NCD) of the recently introduced 5th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5), with (age-associated) cognitive impairment falling under the category Mild NCD and mild dementia falling under the category Major NCD. Actually, the inclusion diagnoses of most clinical trials of standardized Ginkgo biloba extract in (aging-associated) cognitive impairment and dementia can be classified under the DSM-5 categories Mild NCD or Major NCD. Both the WEU indication and the clinical evidence for standardized Ginkgo biloba extract are thus in line with the current concept of neurocognitive disorders. We kindly request, however, the inclusion of the indications Peripheral Arterial Occlusive Disease (intermittent claudication), adjuvant therapy in tinnitus of vascular and involutive origin and vertigo of vascular and involutive origin. Clinical data on these indications, which comply with the criteria for the "well-established use", have already been submitted to the HMPC. The indications are approved indications in numerous member states. Furthermore, as the basic THMP requirements are not met ("*the product is not harmful under normal conditions of use*"), we disagree with the use of "Powdered herbal substance" as active ingredient of THMP products. Detailed comments see below.	The indication in the monograph is to be understood in total and should not be separated in partial sections. Not endorsed. (see below) Not endorsed. (see below)
Weleda AG	<u>Rational for Traditional Use of the liquid extract prepared from fresh *Ginkgo biloba* L. folium (DER 1:2-3), extraction solvent: ethanol 65% V/V</u> Historically Ginkgo tinctures have been produced since at least 1950 by the homeopathic laboratories but their use was always a merely traditional herbal use, which is reflected also in the indication and in the fact that there is no homeopathic use for this tinctures. Therefore this liquid extracts should be considered as traditional use in herbal medicine. The liquid extract from Ginkgo fresh leaves prepared by using ethanol 65% V/V (DER 1:2-3), called "tincture" or "MT" in the literature, is on the French market since 30 years with a continuous use, as can be seen on: - Excerpt from 1984 French Health ministry decision, showing that the liquid extract from Ginkgo leaves in the form of oral drops could be marketed by Laboratories Weleda as pharmaceutical products [1] - Product related documentation, i.e. sales catalogues or reference product catalogues from several Herbal medicinal products laboratories: Laboratoires Weleda 1999 [2],	Not endorsed. The monograph is based on the herbal substance as defined in the Eur. Ph. and is not including fresh starting material. The references provide a tradition in homeopathy. The references on use in phytotherapy are not demonstrating the usage of the specific extract. No data are provided to substantiate posology and DER.

Interested party	Comment and Rationale	Outcome
	Laboratoires Lehning 1984 [3], Laboratoires Boiron 1985 [4] and 2007 [5], Laboratoires LHF 1950 [6]. Indeed, before standardized concentrate extracts from *Ginkgo biloba* leaves have been marketed in several European countries with clinical data linked to, Ginkgo leaves were also available in France as traditional herbal preparations for oral administration, in particular as hydroalcoholic extract. Therefore, the use of *Ginkgo biloba* L. leaves in alcohol is described in a reference Phytotherapy handbook from 1961 "Ressources Médicinales de la Flore Française" already indicating a potential effect on blood flow that complies with the traditional use therapeutic indication from the draft monograph [7]. The same use is also found in a more contemporary (2007) Phytotherapy handbook "Phytothérapie la santé par les plantes". This handbook indicates the use of the liquid extract (tincture) in troubles associated with circulatory disorders at a posology of 100 drops twice a day ; in particular flavonoids* are responsible for this therapeutic activity [8]. This posology is coherent with the traditional use posology given in the draft community monograph: 750 mg of powdered Ginkgo leaf daily. In fact, 1 ml of liquid extract (tincture) corresponds to 20 drops. So, the handbook daily dose of 200 drops = 10 ml of liquid extract = 9,6 g of liquid extract = 960 mg of leaf expressed as dried drug daily. Ethanol is widely used as an extraction solvent and would not modify the safety profile of Ginkgo leaf given in the monograph. Therefore, except an appropriate labeling for the ethanol content, specific information on safe use is not expected to be different from what is stated in the daft community monograph for the powder. * Flavonoids represented by isoquercitrin are routinely measured	

Other comments have been received on details of the assessment report but not relating to the draft monograph. All these comments have been taken into consideration and appropriately addressed in the versions revised after public consultation. However, according to the standard disclaimer at draft assessment reports no overview of comments is prepared in relation to the comments on the draft assessment report.

Additions or corrections of monograph and assessment report are only made if the information is relevant. The monograph is defining a harmonised view. For instance as the availability of information about products in the market is differing and dynamic, the objective of monograph and assessment report is not to provide an exhaustive overview.

Specific comments on text

Well-established use

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	IPSEN PHARMA	**We propose to harmonize the description of the qualitative composition of herbal preparations with the Ph.Eur. monograph as follows:** ii) Herbal preparations Dry extract (DER 35-67:1), extraction solvent: acetone 60% m/m, as characterized by the monograph "GINKGO DRY EXTRACT, REFINED AND QUANTIFIED" (1827) of the European Pharmacopoeia. Rationale: Only Ginkgo Biloba extracts complying with the European Pharmacopoeia can support a Well-established use application in Europe. Therefore, the reference to the European Pharmacopoeia needs to be clear in the herbal monograph.	Endorsed. A reference to the respective monograph is introduced. Irrespective of this clarification data from other herbal preparations are also taken into account for the establishment of the European Union monograph.
2. Qualitative and quantitative composition	Schwabe	**We propose to amend the description of the qualitative composition of herbal preparations by reference to the Ph.Eur. monograph as follows:** **ii) Herbal preparations** **Dry extract (DER 35-67:1), extraction solvent: acetone 60% m/m, as characterized by the monograph "GINKGO DRY EXTRACT, REFINED AND QUANTIFIED" (1827) of the European Pharmacopoeia.** **Rationale:** The well-established use of *Ginkgo biloba* dry extract is based on experience as well as preclinical and clinical data with refined extracts, quantified to a defined content of flavonoids, bilobalide, ginkgolides A, B and C, and limited with regard to	Endorsed. A reference to the respective monograph is introduced. Irrespective of this clarification also data from other herbal preparations are taking into account for the establishment of the European Union monograph.

Section number and heading	Interested party	Comment and Rationale	Outcome
		the content of toxic ginkgolic acids, as characterized in the Ph. Eur. This quantified content of flavonoids and terpene lactones as well as the ginkgolic acids limitation is the basis for the extract's efficacy and tolerability. The provisions of the DER and the solvent for the first extraction step combined with a reference to the herbal quality guidance are absolutely insufficient to characterize the quality of a well-established use *Ginkgo biloba* dry extract. *Ginkgo biloba* dried leaves contain a significant amount of potentially harmful compounds such as ginkgolic acids or biflavones. These substances cannot be adequately removed by extraction with acetone 60% m/m. Moreover, extraction with acetone 60% m/m at a DER of 35-67:1 alone will not yield a sufficient and consistent content of the Ginkgo flavonoids and terpene lactones that have been demonstrated to contribute to efficacy. Therefore, quality according to the Ph. Eur. monograph is a prerequisite for well-established use.	
2. Qualitative and quantitative composition	EUCOPE	Compare comment from Schwabe (2. Qualitative and quantitative composition, well-established use)	Endorsed. A reference to the respective monograph is introduced. Irrespective of this clarification also data from other herbal preparations are taking into account for the establishment of the European Union Monograph.
4.1. Therapeutic indications	IPSEN PHARMA	**Adjunctive treatment of vertigo of vestibular origin in addition to vestibular rehabilitation** Vertigo is characterised by a perception of motion, such as feeling the room spinning when the subject is stationary. Dizziness refers to a feeling of light-headedness or of loss of balance. These symptoms may arise as a consequence of dysfunction of the vestibular system in the inner ear. The term 'vestibular vertigo' covers a number of specific vestibular disorders, of which the four most frequent are benign	Not endorsed. The available data have been evaluated and in summary, an indication in this field was not accepted because of the inconsistency of the data. The justification presented is selective – especially those studies supporting the suggestion are from the 1980ies and 90ies. Adjunctive treatment in vertigo has not been investigated as a primary objective.

Section number and heading	Interested party	Comment and Rationale	Outcome
		paroxysmal positional vertigo (BPPV), vestibular migraine, Ménière's disease, and vestibular neuritis [1]. Dizziness and vertigo rank among the most common symptoms in medical practice and are among the ten most common reasons for a neurological examination [2]. Vertigo is a frequent symptom in the general population with a 12-month prevalence of 5% and an incidence of 1.4% in adults. Its prevalence rises with age and is about two to three times higher in women than in men. Follow-up studies have shown benign paroxysmal positional vertigo recurrence rates of 50% at five years and a persistence of dizziness related to anxiety in almost a third of patients one year after vestibular neuritis [3]. Vertigo has potentially devastating effects on a person's day-to-day functioning, ability to work, relationships with family and friends, and quality of life [4]. **Current treatment and unmet medical needs** In both Ménière's disease and vestibular neuritis, vestibular suppressants such as anticholinergics and benzodiazepines are used [5]. In Ménière's disease, salt restriction and diuretics are used in an attempt to prevent flare-ups. In vestibular neuritis, only brief use of vestibular suppressants is now recommended. Vestibular migraine can be treated with standard antimigraine therapies [20]. However, drug treatments are not presently recommended for BPPV and bilateral vestibular paresis, but physical therapy treatment can be very useful in both. In particular, vestibular rehabilitation exercises are the recommended treatment option in BPPV [6]. **Data supporting the efficacy of EGb761®** The utility of EGb761® in the treatment of vertigo has been evaluated in eight randomised, placebo controlled, double-blind studies [7, 8-13]. These studies evaluated EGb761® in vestibular vertigo (three studies), non-vestibular vertigo (two studies), and mixed vertigo types (two studies). These studies are listed in Table 1 below.	The clinical relevance of the studies cited now in the comment was not convincing to modify the position of the HMPC.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Studies in non-vestibular vertigo and studies including mixed populations with both types of vertigo will not be considered here. The three studies in vestibular vertigo also compared EGb761® to placebo and included 155 patients between them. Two used sway amplitude, an objective and validated outcome measure, and the third study a patient-reported outcome measure [7]. In one of the studies, all patients underwent vestibular rehabilitation therapy [9]. Moreover, a systematic review published in 2007 [14] has evaluated all randomised, placebo controlled, double-blind studies performed in patients with vertigo. This evaluated all randomised, double-blind, controlled studies of EGb761® in vestibular and non-vestibular vertigo. Only studies in which vertigo was an inclusion criterion rather than a concomitant symptom were taken into consideration. Five such studies were considered, including the three individual studies discussed above. The author concluded that the clinical efficacy of EGb761® in vestibular and non-vestibular vertigo had been demonstrated in randomised, placebo-controlled, double-blind studies, and that these studies provided convincing evidence of the efficacy of EGb761® in vertiginous symptoms. There is also a substantial amount of preclinical data showing that EGb761® can hasten improvement of symptoms and recovery of vestibular compensation after unilateral vestibular damage in rats, cats and guinea-pigs [15-19]. **Conclusion:** The efficacy of EGb761® in vestibular vertigo has been demonstrated in three randomised, placebo-controlled studies which, taken together, provide convincing evidence of the efficacy of EGb761® in vertiginous syndromes. These studies measured outcome in terms of the severity of clinical vertigo symptoms, subjectively assessed by the patient, as well as of the objective measure of sway amplitude, which reflects vertigo severity and the risk to the patient. These measures are considered as relevant parameters for assessing the efficacy of anti-vertigo drugs.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		However, since vestibular rehabilitation is an established and recommended therapy for vestibular vertigo, we propose that EGb761® could be indicated as adjunctive therapy to vestibular rehabilitation, in order to ensure that prescription of EGb761® does not deprive patients of the opportunity to benefit from vestibular rehabilitation. This is supported by the demonstration of an added benefit of EGb761® when given with vestibular rehabilitation in one of the studies reviewed above [9].	
4.1. Therapeutic indications	IPSEN PHARMA	**Symptomatic treatment of Tinnitus** Tinnitus is a common condition, with a life-time prevalence of around 10% [1]. Severe disabling tinnitus may occur in around 5 per thousand subjects in the general population. Persistent severe tinnitus may cause irritability, fatigue and depression [2], and is associated with impaired quality of life [3]. Currently, no medications have been validated or approved for the treatment of tinnitus and medical needs are essentially unmet [4]. Antidepressants are the only drug class to show any possible benefit [5], although well-controlled clinical trials remain to be performed, and the available evidence is equivocal [5, 6]. Nonpharmacological treatments include transcranial magnetic stimulation, sound masking therapy, tinnitus retraining therapy and cognitive behavioural therapy. Of these treatments, the evidence is strongest for cognitive behavioural therapy [5, 7]. However, the efficacy of these non-pharmacological treatments remains poorly established [198]. Several randomised, controlled clinical studies of EGb761 in the treatment of tinnitus have demonstrated a statistically significant superiority of treatment with EGb761 over placebo or active comparator when used over a period of 1 to 12 months. Two of these used audiometric outcome measures [8, 9], and these findings are the most reliable. The outcome measures evaluated in the studies include both audiometric and patient-reported qualitative measures, which are both	Not endorsed. The available data have been evaluated and in summary, an indication in this field was not accepted because of the inconsistency of the data. The clinical relevance of the studies cited now in the comment was not convincing to modify the position. Limited data cannot be transferred to all Tinnitus patients and a longer duration of use.

Section number and heading	Interested party	Comment and Rationale	Outcome
		clinically relevant for determining the potential benefit of treatment. In these studies discussed above, both types of outcome measure were improved by treatment by EGb761. The change in tinnitus volume reported in the studies which have used an audiometric outcome measure (between 5 and 10 dB) is considered to be clinically relevant [10]. There is no reason to think that the benefit observed cannot be generalised to all patients with persistent tinnitus. In one study that investigated prognostic factors [11], no association was observed between the size of the treatment effect of EGb761 and time from onset, laterality and periodicity of tinnitus. However, another larger study from the same group [12] reported that response rates were higher in patients with intermittent, unilateral or recent-onset tinnitus, although the treatment effect size was similar. No attempt to grade symptoms by severity was made with respect to the eligibility criteria of any of these studies. One recent observational study in a real-world treatment setting [13] has provided evidence that EGb761 provided a sustained beneficial effect on subjective tinnitus throughout an observation period of 12 months. The evidence for a benefit of EGb761 in the treatment of tinnitus reposes as well on a large recent study in patients with dementia, in which tinnitus was evaluated as a secondary outcome measure [14]. An important strength of the 2 tinnitus studies using audiometric measures of tinnitus [8, 9] was that there was little evidence for a placebo effect. Tinnitus thresholds evolved only marginally over the course of the study in both studies and in the study which measured hearing acuity [15], hearing loss deteriorated in the placebo group, whilst it improved in the EGb761 treatment group. The absence of a placebo effect increases the confidence with which the treatment benefit of EGb761 can be interpreted. Some uncertainty surrounding the benefit arises from the existence of some negative studies. A large (978 patients enrolled), placebo-controlled study of another Ginkgo biloba	

Section number and heading	Interested party	Comment and Rationale	Outcome
		extract (LI-1370) which has the same composition in terms of active ingredients to EGb761 [15]. This study provided no evidence for any benefit of LI-1370, although it should be noted that audiometric outcomes were not determined in this study. In addition, a recent comparative study of clonazepam and EGb761 in patients with tinnitus failed to demonstrate any beneficial effects of EGb761 [16]. Although this study evaluated both objective audiometric outcomes and patient reported outcomes, it was neither placebo-controlled nor blinded, which limits the strength of evidence provided by this study. In conclusion, **EGb761 would be expected to be used in the symptomatic treatment of tinnitus**, which has an incidence of around 0.5% in the general population. Since this is a chronic condition, treatment would be given for extended periods, and the safety profile of EGb761 is acceptable for long-term use in the community. Effective treatment of tinnitus may provide substantial benefits in terms of reduction of the disability associated with tinnitus. Alternative effective treatments for tinnitus remain very limited and EGb761 can thus fulfill an important unmet medical need.	
4.1. Therapeutic indications	Schwabe	**4.1. Therapeutic indications** **For the reasons given below we kindly request the inclusion of the following therapeutic indications under "well-established use":** • **peripheral arterial occlusive disease (intermittent claudication)** • **adjuvant therapy in tinnitus of vascular and involutive origin** • **vertigo of vascular and involutive origin** **Rationale**	Not endorsed. The available data have been evaluated and in summary, an indication in these fields was not accepted because of the inconsistency of the data. Results and defaults of all studies were considered. The article about the new study by Sokolova *et al.* (2014, in press) is limited in its information, e. g. not clearly presenting primary objectives, rationale for evaluation of centres involved etc. The clinical relevance of the studies cited now in the comment was not convincing to modify the position.

Section number and heading	Interested party	Comment and Rationale	Outcome
		According to Guideline EMEA/HMPC/104613/2005: "In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy" for "well-established use". The available clinical data from randomized, placebo-controlled trials of Ginkgo biloba dry extract, which were already submitted in response to the call for data, thus comply with the criteria for "well-established use" given in this Guideline. From the draft assessment report released on 28 January 2014 it would appear that the evaluation of these three indications has been biased by relying too much on data from trials and reviews that may not be state of the art or were not focusing on monograph-compliant extracts. On the other hand, the findings of randomized, placebo-controlled trials with the high-quality extract EGb 761® appear to have been given too little weight. The rationale in support of well-established use in the three indications is given in detail in attachment 1 and is summarized as follows: **<u>Peripheral arterial occlusive disease</u>** The evaluation of the efficacy of Ginkgo biloba extract, EGb 761® in particular, does not appear to take the shortcomings of the Cochrane Review by Nicolaï et al. (2009), and some of the trials included, fully into account. When evaluating efficacy of Ginkgo biloba dry leaf extracts manufactured with a DER and an extraction solvent as characterized in the draft monograph, only those clinical trials should be considered that were conducted with corresponding extracts. Clinical trials conducted with extracts not meeting these requirements are not pertinent to the monograph. Importantly, the Ginkgo products used in two negative trials in PAOD (Drabaek et al. 1996, Wang et al. 2007) did not meet the monograph requirements. If these trials are excluded from the review, a clearly positive result for extracts manufactured according to Ph. Eur. (such as EGb	

Section number and heading	Interested party	Comment and Rationale	Outcome
		761®) would be found. This would justify the inclusion of the therapeutic indication peripheral arterial occlusive disease (intermittent claudication) for well-established use in the monograph. **<u>Adjuvant therapy in tinnitus of vascular and involutive origin</u>** Unfortunately, two placebo-controlled randomized double-blind clinical trials (Morgenstern and Biermann 1997, Meyer 1986) that were submitted during the call for data have not been considered in the assessment report. The evaluation of the efficacy of Ginkgo biloba extract for this indication , specifically EGb 761®, does not appear to take into account that extracts other than those manufactured according to Ph. Eur. were included in the Cochrane Reviews by Smith et al. (2005) and Hilton and Stuart (2010) and the meta-analysis by Rejali et al. (2004). Nor were the serious shortcomings of some of the trials (Holgers et al. 1994, Drew and Davies 2001, Rejali et al 2004) adequately taken into consideration. When evaluating efficacy of Ginkgo biloba dry leaf extracts manufactured with a DER and an extraction solvent at a specified daily dose as characterized in the draft monograph, only those clinical trials should be considered, that were conducted with corresponding extracts and doses. Clinical trials conducted with extracts or daily doses not meeting these requirements are not pertinent to the monograph. Importantly, the Ginkgo products used in two negative trials in tinnitus (Rejali et al. 2004, Holgers et al. 1994) did not meet the monograph requirements. For example, a trial conducted with a daily dose of 29.2 mg can only be of limited relevance for a monograph specifying daily doses of 120 to 240 mg Ginkgo biloba dry extract. Therefore the present evaluation of efficacy for adjuvant therapy in tinnitus of vascular and involutive origin does not adequately reflect the clinical data. Excluding the methodologically flawed trials from the review and including all submitted adequate trials, as appropriate, would yield a clearly	

Section number and heading	Interested party	Comment and Rationale	Outcome
		positive result for quantified Ginkgo biloba extracts according to Ph. Eur. at daily doses of 120 to 240 mg. The systematic review of studies of EGb 761® by von Boetticher (2011) underlines the suitability of this therapy for the indication sought and justifies the inclusion of the therapeutic indication adjuvant therapy in tinnitus of vascular and involutive origin for well-established use. **<u>Vertigo of vascular and involutive origin</u>** The evaluation of the efficacy of Ginkgo biloba extract in vertigo, specifically EGb 761®, would appear to be incomplete. Although Ginkgo products have been approved for the treatment of vertigo or dizziness in the EU for decades, vertigo is not even mentioned in section 4.3 of the draft assessment report "*Overall conclusions on clinical pharmacology and efficacy"*. Unfortunately, seven placebo-controlled randomized double-blind clinical trials that were submitted during the call for data have not been considered in the assessment report (Moreau 1975, Schwerdtfeger 1981, Claussen und Kirtane 1985, Hamann 1985, Mangabeira Albernaz 1986, Vorberg et al. 1989, Heide et al. 1998). The comparative study by Issing et al. (2005) and the systematic review by Hamann have not been adequately assessed. The latter, together with the recently completed trial by Sokolova et al. (2014, in press) in patients with vertigo as primary diagnosis, and the findings from three trials investigating effects of EGb 761® in patients with dementia and symptoms of vertigo/dizziness would appear to justify the therapeutic indication *vertigo of vascular and involutive origin* for well-established use.	
4.4. Special warnings and precautions for use	IPSEN PHARMA	See comments and rationale in 4.8 Undesirable effects	Not endorsed. (see 4.8)
4.4. Special	Schwabe	**We propose to replace the warnings**	Not endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
warnings and precautions for use		***"In patients with a pathologically increased bleeding tendency (haemorrhagic diathesis) and concomitant anticoagulant and antiplatelet treatment, the medicinal product should only be used after consultation with a doctor.*** ***Preparations containing Ginkgo might increase susceptibility to bleeding, the medicinal product should be discontinued as a precaution 3 to 4 days prior to surgery."*** **by the following text:** **"Single reports indicate the possibility that Ginkgo-containing preparations could increase bleeding tendency. Clinical studies do not give any evidence of an interference with haemostasis/blood coagulation(EUCOPE)."** **Rationale:** The/This statement in the draft monograph does not reflect the scientific evidence available for refined and quantified extracts manufactured according to Ph. Eur. such as EGb 761®. The warning regarding a potential increase of the bleeding tendency may apply to Ginkgo preparations not manufactured according to Ph. Eur. Such preparations made from *Ginkgo biloba* that are not well standardized are marketed as unregulated health products such as dietary supplements in many countries. These products may contain ginkgo leaf constituents such as ginkgolic acids and biflavones, or even adulterations (Kakigi et al. 2012, Wohlmuth et al. 2014, see attached expert statement) which considerably contribute to undesirable pharmacological effects or pharmacokinetic drug interactions. Data reported from case reports or studies conducted with poorly characterized extracts should therefore not be considered for the well-established use part of the monograph.	During the development of the European Union monograph it has already been discussed that there is broad mix of data. However, there are more than "single" reports and a risk cannot be excluded. The wording in section 4.4 is appropriate as it is defining in each paragraph a specific group of patients for which special care is necessary. [In section 5.1 reduction in platelet aggregation is listed]

Section number and heading	Interested party	Comment and Rationale	Outcome
		In fact, there is no proof from pharmacological or clinical studies that refined and quantified extracts according to Ph.Eur. impair haemostasis or platelet aggregation or enhance the bleeding tendency (s. comments on interactions and on adverse effects). In addition, specific interaction trials with refined and quantified extracts according to Ph.Eur. did not find interactions with anticoagulants or platelet aggregation inhibitors. A comprehensive rationale is provided in attachment 2. Therefore, The proposed text describes the scientific state of knowledge more adequately. **We propose to delete the following warning:** ***"Concomitant use of G. biloba containing products and efavirenz is not recommended (see section 4.5)."*** **Rationale:** There is a lack of scientific evidence that Ginkgo is responsible for the decreased efficacy of efavirenz. This warning is not justified and should be removed from section 4.4 (s. above) as well as 4.5. A comprehensive rationale is provided in attachment 2/ the attached expert statement.	Not endorsed. During the development of the European Union monograph the data have already been discussed and it was decided to introduce a warning. [In section 5.1 reduction in platelet aggregation is listed]
4.4. Special warnings and precautions for use	EUCOPE	Compare comment from Schwabe (4.4. Special warnings and precautions for use)	See above
4.5.	IPSEM	Potential interactions between EGb761® and other medicinal products have been reviewed based on a comprehensive	Not endorsed. (a review is mentioned, a specific

Section number and heading	Interested party	Comment and Rationale	Outcome
Interactions with other medicinal products and other forms of interaction	PHARMA	literature search completed till 11 April 2014 which identified 1-31 published articles or abstracts in English reporting drug interaction studies in healthy volunteers or subjects with pharmacokinetic evaluations. Many of the published pharmacokinetic interaction studies have used different Ginkgo biloba extract preparations to EGb761. Based on review of these publications, there is no consistent evidence that Ginkgo biloba extracts have a clinically relevant pharmacokinetic interaction with drugs metabolised through CYP1A2, CYP2B6, CYP2C9, CYP2D6 or CYP2E1 enzymes, and with P-glycoprotein (PgP) substrates. Importantly, no significant interactions have been reported between Ginkgo biloba extracts and digoxin (PgP substrate), and warfarin (CYP1A2, CYP3A4 and CYP2C9 substrate). **Other clinical studies have shown no effect of Ginkgo biloba extracts on international normalised ratio levels in subjects on warfarin**. At the present time, the reported potential interactions between Ginkgo biloba and CYP2C19 and CYP3A4 substrates are considered to be inconclusive. However, there is some evidence from drug interaction studies that Ginkgo biloba extracts may interfere with the pharmacokinetics of drugs metabolised by CYP3A4; some study results suggested enzyme induction, other studies suggest enzyme inhibition or no significant effect. Despite the current uncertainty, in consideration of a significant number of drugs with narrow therapeutic index which are metabolized via CYP3A4, the MAH considered it prudent and appropriate to advise a general caution relating to the concomitant use of drugs with narrow therapeutic index which are metabolised via CYP3A4 with EGb761®. **However the MAH do not evidence any concern regarding concomitant intake of EGb761 with anticoagulants or antiplatelet drugs which could indicate their effect may be influenced.** **Available studies with warfarin do not indicate that there**	reference is not given) During the development of the European Union monograph the data have already been discussed and it was decided to introduce appropriate information in the interaction section. Especially for preparations derived from Ginkgo biloba leaves there is a mix of evidence on interactions, reports and preliminary pharmacodynamics considerations.

Section number and heading	Interested party	Comment and Rationale	Outcome
		is an interaction between warfarin and G. biloba products.	
4.5. Interactions with other medicinal products and other forms of interaction	Schwabe	**We propose to replace the wording in the draft monograph by the statement** **"No clinically relevant interactions have become known up to now."** **Rationale:** There is a lack of scientific evidence for interactions of refined and quantified *Ginkgo biloba* extracts according to Ph. Eur. with other medicinal products. A comprehensive rationale is provided in attachment 2/the attached expert statement.	Not endorsed. During the development of the European Union monograph the data have already been discussed and it was decided to introduce appropriate information in the interaction section. Especially for preparations derived from Ginkgo biloba leaves there is a mix of evidence on interactions, reports and preliminary pharmacodynamics considerations.
4.5. Interactions with other medicinal products and other forms of interaction	EUCOPE	Compare comment from Schwabe (4.5. Interactions with other medicinal products and other forms of interaction)	See above
4.6. Fertility, pregnancy and lactation	Schwabe	**Pregnancy** **We propose to delete the statement:** **"G. biloba extracts may impair the ability of platelets to aggregate. The tendency for bleeding may be increased."** **Rationale:** There is no proof from pharmacological or clinical studies that refined and quantified extracts according to Ph. Eur. may impair the ability of platelets to aggregate or enhance the	Not endorsed. See also section 4.4

Section number and heading	Interested party	Comment and Rationale	Outcome
		bleeding tendency (please refer to section 4.4 Special warnings and precautions for use). **We propose to delete the statement: "Animal studies are insufficient with respect to reproductive toxicity (see section 5.3)."** This statement is incorrect as non-clinical data from conventional studies of reproduction and development are available and reveal no special hazard for humans. In segments I to III reproductive and developmental toxicity studies, Ginkgo extract EGb 761® has been tested following oral administration at doses of 100, 400 and 1600 mg/kg in rats and 100, 300 and 900 mg/kg in rabbits. At these dosages Ginkgo extract EGb 761® has not been observed to elicit any teratogenic or other detrimental effects on fertility or reproductive performance (DeFeudis 1998; see Assessment Report). Furthermore, the effect of EGb 761® (100, 350 and 1225mg/kg/day) on embryo-foetal development in mice during the critical period of organogenesis was evaluated in a recently published study. During external and internal inspection of the foetuses as well as examination of skeletal and soft tissues, no embryotoxic properties were noted. In particular, the incidence of malformations, variations or retardations was not increased and the general condition of dams was not influenced. Thus, the no-observed-effect level (NOEL) was above 1225 mg/kg/day for the dams and the foetuses (Koch et al. 2013). **<u>Fertility</u>** **We kindly request to delete the sentence: "In a study in female mice effects on fertility were seen (see section 5.3)."** **Rationale:** The draft monograph refers to a study in female mice in which	Not endorsed. Not endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		effects on fertility were seen. This study is further referred to in some more detail in section 5.3. where it is stated that Ginkgo extract EGb 761® caused significantly reduced ovarian follicle counts, reabsorption index, implantation index and foetal viability at a dose of 14.8 mg/kg/day. The credibility of the study suffers strongly from the insufficient quality and the definitely incorrect designation of the extract that was tested. The authors of the study publication state that the extract was obtained from an Egyptian pharmaceutical company in the form of capsules containing 260 mg of extract. This company, however, is not a licensee of the manufacturer of EGb 761®. Furthermore, EGb 761® is not available as capsules but only as film-coated tablets containing a maximum of 240 mg extract. Analyses of different batches of the preparation from this Egyptian company revealed that the extract is clearly adulterated by the addition of flavones and, more importantly, contains high concentrations of ginkgolic acids (data available on request). In view of this, it has to be concluded that *Ginkgo biloba* extract EGb 761® was definitely not used in their investigations and it is unlikely that the extract used complies with Ph. Eur (Koch et al. 2013). This suggests a violation of the standards of scientific conduct. Moreover, this publication is not relevant for the topic of this WEU monograph concerning refined and quantified extracts. We would therefore like to suggest that reference to this publication be deleted from both 4.6 and 5.3.	
4.6. Fertility, pregnancy and lactation	EUCOPE	Compare comment from Schwabe (4.6. Fertility, pregnancy and lactation)	See above
4.8. Undesirable effects	IPSEN PHARMA	Some concern about a possible association between use of Ginkgo biloba extracts and an increased risk of bleeding was raised by the publication between 1996 and 2004 of eighteen case-reports pertaining to the emergence of haemostasis disorders in patients treated with a variety of Ginkgo biloba preparations.	Not endorsed. During the development of the European Union monograph it has already been discussed that there is broad mix of data. However, there are many reports on

Section number and heading	Interested party	Comment and Rationale	Outcome
		This issue has been addressed in three publications [1-3] which have described randomised, double-blind controlled studies designed to assess the effect of Ginkgo biloba extract on platelet function and bleeding time. A specific study was dedicated to the exploration of platelet function and coagulation in healthy volunteers treated with EGb761® [1]. A prospective, double-blind, randomised, placebo-controlled study design was used. The study compared treatment with doses of 120, 240 and 480 mg/day for fourteen days. No differences were revealed between any of the EGb761® treatment groups and the placebo group in platelet function, fibrinolysis or coagulation All three studies concurred that Ginkgo biloba had no adverse effect on platelet function and bleeding time. In addition to these studies in healthy volunteers, a more recent study in 67 patients with PAOD enrolled in a randomised, placebo-controlled clinical trial of EGb761® [4] failed to detect any difference in platelet activation or aggregation between the placebo and EGb761® treatment groups [5]. Finally, a randomised open-label trial has been performed at the request of the Korean Health Authorities in order to evaluate potential pharmacodynamic and pharmacokinetic interactions between ticlopidine and EGb761® [6]. Bleeding times and platelet function did not differ between the ticlopidine alone and ticlopidine/EGb761® treatment groups. Similarly, EGb761® did not modify the pharmacokinetic properties of ticlopidine. Haemostasis parameters were specifically studied in two large randomised clinical trials of EGb761®. The first was a large randomised comparative trial of EGb761® performed in the United States which included 513 patients [7] developed to assess the efficacy and safety of EGb761® in patients with Alzheimer's disease. The clinical program showed that there were no statistically significant difference in laboratory tests nor in the frequency of adverse events potentially related to haemostasis between patients treated with EGb761® (169 patients treated with 120 mg/day; 170 patients treated with 240 mg/day) and placebo (174 patients) for 26 weeks.	bleedings and a risk cannot be excluded.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Furthermore, no between-group differences in the frequency of haemorrhagic events could be observed in subgroups of patients concomitantly taking aspirin or warfarin. The second study was the GuidAge study [8], in which 2854 subjects were randomised to treatment for five years with either EGb761® 120 mg twice a day or a matching placebo. In the GuidAge study, the overall incidence of haemorrhagic events in the EGb761® and placebo groups was similar at 9.4% and 9.1%, respectively. Review of all reported haemorrhagic events, by SOC and PT, showed no differences between the EGb761® and placebo groups. There were no SAEs describing haemorrhagic events that were considered by the investigator as related to EGb761®. In addition, at the request of the FDA, haemorrhagic events were thoroughly documented in the GEM study [9], a six-year prevention study in which 1524 subjects were exposed to a dose of EGb761® of 120 mg bid. In this study, rates of major bleeding did not differ between the treatment groups (HR: 0.97 [0.77 – 1.23] and bleeding incidence did not differ for individuals taking aspirin and assigned to either EGb761® or placebo (rates of 1.98 and 1.76 per 100 person-years, respectively, p = 0.44). Although there were twice as many haemorrhagic strokes in the EGb761® group compared with the placebo group (16 versus 8), the number of cases was small and non-significant in the analysis (p = 0.12). A meta-analysis was published in 2011 with the goal of determining the effect of standardized Ginkgo biloba leaf extracts on outcome parameters of haemostasis associated with risk of bleeding [10]. Eighteen randomised controlled trials in a variety of indications were considered, which included between them 1985 patients. Random-effects models of effects on baseline change or mean difference showed a positive effect of Ginkgo biloba extract on blood perfusion, as shown by a significant reduction in blood viscosity (WMD -1.03 mPa•sec, 95% CI -1.29 to -0.78 mPa•sec), but no evidence of any significant effect on ADP-induced platelet aggregation (WMD -0.35%, 95% CI -15.16-14.46%), fibrinogen concentration (GIV	

Section number and heading	Interested party	Comment and Rationale	Outcome
		- 2.45 mg/dl, 95% CI -11.59-6.70 mg/dl), aPTT (GIV -0.42 sec, 95% CI -0.97-0.12 sec), and PT (SMD 0.00, 95% CI -0.09-0.09). Subgroup analyses revealed a statistically significant reduction in aPTT for subgroups receiving high-dose Ginkgo biloba extract at 240 mg/day or more (GIV -0.47 sec, 95% CI -0.88 to -0.05 sec) and for studies including only patients, not healthy volunteers (GIV -0.61 sec, 95% CI -0.95 to -0.27 sec); however, none of these findings were considered clinically relevant. A search of PubMed (MEDLINE) to support review of this topic largely revealed case reports of haemorrhagic events in patients using Ginkgo biloba that were already in the Company's global safety database and constitute the literature cases discussed in this review. With one exception, it is not clear from the 24 literature cases of haemorrhagic reactions if the Ginkgo biloba extract used was manufactured by Ipsen Pharma. In only one case was it specified that the product used was EGb761®. Other products may have different properties, particularly if combined with other supplements. The events most frequently reported in the literature were cerebral haemorrhage (six cases), post procedural haemorrhage (four cases) and subdural haematoma (four cases). Two cases of intracranial bleeding have been described after long-term use of a Ginkgo biloba extract, one of which was fatal [11, 12]. In addition, a prescription claims database survey performed in Taiwan has explored the risk of haemorrhage associated with coprescriptions for Ginkgo biloba extracts and antiplatelet or anticoagulant agents, and evaluate the trends of co-prescriptions [13]. Over 20 000 prescriptions were evaluated. It was concluded that the combination of Ginkgo biloba extract with antiplatelet or anticoagulants showed an insignificant correlation with the risk of haemorrhage. In the Ipsen Global Drug Safety database, a total of 137 individual haemorrhagic adverse events had been reported in 122 patients (74 serious cases and 48 non-serious cases) to	

Section number and heading	Interested party	Comment and Rationale	Outcome
		the Company since the IBD (24 January 1975 (France)) and up to 31st January 2012. The SOCs with the highest numbers of individual haemorrhagic events were eye disorders (26 events), respiratory, thoracic and mediastinal disorders (20 events) injury, poisoning and procedural complications (18 events), and nervous system disorders (18 events). The most frequently reported individual haemorrhagic adverse events were epistaxis (17 events), retinal haemorrhage and haematoma (12 events each), cerebral haemorrhage (10 events), subdural haematoma (7 events each) and coagulopathy (6 events). Review of the serious cases showed that in addition to their advanced years, the majority of patients had at least one risk factor for bleeding, such as retinal radiotherapy, hypertension, concomitant use of drugs bearing an identified haemorrhagic risk (eg aspirin, warfarin,fluindione, steroids, vitamin E or rofecoxib), previous surgery, head injury or a family history of haemorrhagic events. It was concluded, based on healthy volunteer studies, studies in patients, meta-analyses of haemostasis outcomes and pharmacovigilance data**, that there was no apparent higher bleeding risk associated with standardised Ginkgo biloba extracts. In addition, there is no evidence for an elevated haemorrhagic risk specifically associated with EGb761**	
4.8. Undesirable effects	Schwabe	**We propose to amend the wording of this section as follows:** **Blood and lymphatic system disorders** **Bleeding of individual organs were reported. The frequency is not known.** **Nervous system disorders** **Headache. The frequency is not known** **Gastrointestinal disorders** **Diarrhoea, abdominal pain, nausea, vomiting. The frequency is not known**	Not endorsed. Frequencies have been calculated from existing clinical data.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Skin and subcutaneous tissue disorders **Uncommon: Allergic skin reactions (erythema, oedema, itching and rash)** A comprehensive rationale is provided in attachment 2/ the attached expert statement.	
4.8. Undesirable effects	EUCOPE	Compare comment from Schwabe (4.8. Undesirable effects)	See above
5.1. Pharmaco-dynamic properties	Midas Pharma GmbH	The mode of action is only enforced by the results of one study: "Human pharmacological data show increased EEG vigilance in geriatric subjects, reduction in blood viscosity and improved cerebral perfusion in specific areas in healthy men (60-70 years) and reduction in platelet aggregation. Additionally, vasodilating effects on forearm blood vessels causing increased regional blood flow are shown." **We propose to add the results from a series of preclinical studies to section 5.1. as follows:** "In preclinical studies *Ginkgo biloba* extract has been shown to exert • Neuroprotection by ○ Improvement of blood fluidity with optimised microcirculation and improved supply of neurons and CNS with nutrition ○ Antioxidative protection of tissues and cells even under stress conditions by scavenging free radicals ○ Tolerance to hypoxia, probably by improved blood flow and energy metabolism ○ Anti-oedema effects • Enhancement of cognitive properties by ○ Effects on neurotransmitters and their receptors, followed by improved learning and memory capabilities	Not endorsed. The European Union monographs are rather moderate in mentioning pharmacodynamics properties. The HMPC acknowledges that for Ginkgo biloba leave preparations a huge amount of data have been published. However, with respect to the nature of multi-component mixtures and the incomplete information on targets, bioavailability and transferability of data it is appropriate to state that the exact mechanism of action is not yet known.

Section number and heading	Interested party	Comment and Rationale	Outcome
		○ Induction of neurogenesis and synaptogenesis" The list of publications referred to is provided in ANNEX 1 (a)	
5.1. Pharmaco-dynamic properties	Schwabe	**We propose to delete the sentence "The exact mechanism of action is not known".** **Rationale:** This sentence does not reflect the fact that EGb 761®, an extract from leaves of *Ginkgo biloba*, is among the most widely used and thoroughly investigated phytopharmaceuticals worldwide. Pharmacodynamic investigations have been published in several hundred scientific articles and important mechanisms of action (such as reduction of blood viscosity, improved neuronal networking) have been sufficiently characterized and are well known. As herbal medicinal products are multi-component mixtures they usually dispose of more than a single mode of action. Thus, the text "the exact mechanism is not known" which implies only one mechanism of action appears not to be appropriate. **We further propose to amend the section on pharmacodynamic properties as follows:** ***"Human pharmacological data show increased EEG vigilance in geriatric subjects, reduction in blood viscosity and improved cerebral perfusion in specific areas in healthy men (60-70 years) and reduction in platelet aggregation. Additionally, vasodilating effects on forearm blood vessels causing increased regional blood flow are shown.*** ***Animal pharmacological data showed improvement of neuronal networking comprised of increase in synaptic connections, neurogenesis and normalization of neurotransmission (dopamine/noradrenalin).*** ***In-vitro data also point to amelioration of cerebral***	Not endorsed. The European Union monographs are rather moderate in mentioning pharmacodynamics properties. The HMPC acknowledges that for Ginkgo biloba leave preparations a huge amount of data have been published. However, with respect to the nature of multi-component mixtures and the incomplete information on targets, bioavailability and transferability of data it is appropriate to state that the exact mechanism of action is not yet known.

Section number and heading	Interested party	Comment and Rationale	Outcome
		energy metabolism and mitochondrial function, antiapoptotic and neuroprotective effects. Also, scavenging of free radicals and inhibition the formation of radical species contributes to the pharmacological activity of Ginkgo biloba dry extract." **Rationale:** Numerous pharmacological effects have been observed and described in scientific publications. They all contribute to the efficacy of EGb 761®. The most relevant ones have been displayed in the above proposed text. Pharmacodynamic properties of *Ginkgo biloba* leaf extracts have recently been comprehensively evaluated in systematic reviews (e.g. Spiess et al. 2011; Lang et al. 2013). "Reduction in platelet aggregation" has so far not been shown at recommended therapeutic doses in humans but only in-vitro. Therefore, it is not a relevant pharmacodynamics property of *Ginkgo biloba* extract. Therefore, we propose to delete this effect.	
5.1. Pharmaco-dynamic properties	EUCOPE	Compare comment from Schwabe (5.1. Pharmacodynamic properties)	See above
5.2. Pharmaco-kinetic properties	Schwabe	**The second sentence** **"Peak plasma concentrations of terpene lactones were in the range of 16-22 ng/ml for ginkgolide A, 8-10 ng/ml for ginkgolide B and 27-54 ng/ml when given as tablets."** **is incomplete and should be revised as follows :** **"….and 27-54 ng/ml for <u>bilobalide</u> when given as tablets".**	Endorsed.
5.2. Pharmaco-kinetic properties	EUCOPE	Compare comment from Schwabe (5.2. Pharmacokinetic properties)	See above

Section number and heading	Interested party	Comment and Rationale	Outcome
5.3. Preclinical safety data	Schwabe	**We propose to replace the wording in the draft monograph by the following statement, according to the QRD template:** **"Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development."** **Should this not be acceptable, we propose to amend this chapter as follows:** **<u>Reproductive toxicity</u>** **We propose to replace the wording in the HMPC monograph by the following text:** **"In segment I to III reproductive and development toxicity studies refined and quantified *Ginkgo biloba* dry extract was tested following oral administration at doses of 100, 400 and 1600 mg/kg in rats and 100, 300 and 900 mg/kg in rabbits and was not observed to elicit any teratogenic or otherwise detrimental effects on fertility and reproductive performance.** **The effect of a refined and quantified *Ginkgo biloba* dry extract (100, 350 and 1225mg/kg/day) on embryo-foetal development in mice during the critical period of organogenesis was evaluated. During external and internal inspection of the foetuses as well as examination of skeletal and soft tissues, no embryotoxic properties were noted. In particular, the incidence of malformations, variations or retardations was not increased and the general condition of dams was not influenced. Thus, the no-observed-effect level (NOEL) was above 1225 mg/kg/day for the dams and the foetuses."** **Rationale:**	Not endorsed. In section 5.3 of the HMPC monograph relevant data were introduced especially also with respect to the recent discussion on carcinogenicity. The HMPC is aware that the extract used in the NTP study has a different specification but as there are similarities in the spectrum of constituents the data are considered.

Section number and heading	Interested party	Comment and Rationale	Outcome
		We strongly disagree with the sentence "*G. biloba* has not been systematically evaluated for its capacity to cause teratogenic effects." and kindly request its deletion. It is not clear whether the term "*G. biloba*" is used here as a synonym for *Ginkgo biloba* dry extract which is subject to the well-established use part of the draft monograph. In fact, an herbal preparation according to the specification for well-established use products (*Ginkgo biloba* leaf extract EGb 761®) has indeed been comprehensively evaluated for potential teratogenic effects in two animal species. In GLP compliant studies EGb 761® was orally administered to rats at doses of 100, 400, 1600 mg/kg from days 7 to 17 of pregnancy and to rabbits at doses of 100, 300, 900 mg/kg from days 8 to 18 of pregnancy. No test substance-related effects on litter parameters or embryonic/foetal development were observed in either study (DeFeudis 1998, see Assessment Report). These studies therefore counter the suggestion that *Ginkgo biloba* leaf extracts have not been systematically evaluated for their capacity to cause teratogenic effects. Also please refer to our argumentation in section 4.6. "Fertility, pregnancy and lactation". Also, we disagree with the inclusion of the results of two studies in this chapter of the draft monograph: In the in the first study, administration of a Ginkgo extract to pregnant rats was reported to produce a decrease in foetal weight at doses of 7 and 14 mg/kg/day in the absence of maternal toxicity (Pinto et al. 2007, see Assessment Report). The extract used was supplied by a Chinese company and contained 28.2% of Ginkgo flavone glycosides and 8.3% of terpene lactones. It was, therefore, clearly outside the specification of the European Pharmacopoeia which requires a content of Ginkgo flavone glycosides of 22.0-27.0% and of terpene lactones of 5.4- 6.6%. Moreover, key data for extract characterization such as extraction solvent or DER are not declared. For these reasons, reference to this publication with respect to *Ginkgo biloba* leaf extracts manufactured according to the European Pharmacopoeia is not appropriate.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		The same applies to an abstract in which the influence of an unspecified extract on the development of chick embryos is described (Floissac and Chopin 1999, see Assessment Report). Both of these references should be removed as they are not relevant to Ph. Eur.-conform extracts for well-established use. **<u>Carcinogenicity</u>** **We propose to amend the sentence** **"It was positive for gene mutation in bacteria and equivocal and negative for chromosome mutations in two separate in vivo tests in peripheral erythrocytes and bone marrow cells in mouse."** **into** **"It was positive for gene mutation in bacteria. A peripheral mouse erythrocytes micronucleus test provided a negative result in male and an equivocal result in female animals."** **Rationale:** The extract was not tested in two separate *in vivo* genotoxicity tests in peripheral erythrocytes and bone marrow cells, but only in one peripheral blood micronucleus test in male and female B6C3F1/N mice following treatment for 3 months. A negative result was obtained in males, while the test was judged to be equivocal in females, although this was based solely on a significant trend test. **Within the sentence** **"A carcinogenicity study was conducted on a *Ginkgo biloba* extract similar to the monograph relevant extract."** **we propose to replace the words "similar to" by "significantly different from".** **Rationale:**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		The draft monograph extensively refers to the NTP Technical Report 578 on the toxicology and carcinogenesis studies of a *Ginkgo biloba* extract (CAS No. 90045-36-6) in F344/N rats and B6C3F1/N mice (gavage studies). The extract used in these studies is described as being similar to monograph-relevant Ginkgo leaf extracts. However, the *Ginkgo biloba* leaf extract discussed in TR-578 is unique and not at all representative of extracts manufactured according to the European Pharmacopoeia such as EGb 761® (CAS No. 122933-57-7). Its content of constituents (31% flavone glycosides, 15% terpene lactones and 10 ppm ginkgolic acids) well exceeds the specifications of the European Pharmacopoeia. In addition, detailed information regarding the manufacturing process (e.g. extraction solvent, ratio of dried plant to solvent, extraction time and temperature, residual solvent, stability etc.) are not declared. Thus, the statement that this extract is "similar to the monograph-relevant extract" is evidently incorrect and misleading and needs to be rectified.	
5.3. Preclinical safety data	EUCOPE	Compare comment from Schwabe (5.3. Preclinical safety data)	See above
Draft Assessment Report (page 39/40) concerning 5.3. Preclinical safety data (single dose toxicity)	Midas Pharma GmbH	General: Section 3.3.1 of the assessment report reflects in large parts results on the isolated compound ginkgotoxin or ginkgolic acid. Ginkgotoxin is mainly found in seeds of *Ginkgo biloba*. Relevant amounts in leaf and leaf extract have not been described. The toxic effects of ginkgolic acid are well known and unquestionable. They are the reason for a strict limitation of the amount of ginkgolic acid tolerated in preparations for human use (<5ppm). It remains unclear, why two of just three papers (Leistner and Drewke, 2010; Liu and Zeng, 2009) referring to "isolated compounds" (impurities) are discussed in section 3.3.1 of the assessment report. Accentuation on the full extract would be appreciated.	The assessment report is summarising the data which contribute to establishing a harmonised view in a European Union monograph. It is mentioned in the disclaimer of the draft assessment report supporting the public consultation on the monograph that the focus is not to comment on the assessment report. If suggestions for changes of the monographs are justified and substantiated with references, the suggestions are discussed and if finally endorsed the relevant documents will be amended. With respect to the existing literature it is not the objective to include all publications. If appropriate

Section number and heading	Interested party	Comment and Rationale	Outcome
			specific references are added.
Draft Assessment Report (page 40-42) concerning 5.3. Preclinical safety data (genotoxicity and carcinogenicity)	Midas Pharma GmbH	Genotoxicity: a series of published and unpublished (Study Report: Salmonella typhimurium and Escherichia coli Reverse Mutation Assay with Ginkgo biloba leaf dry extract. Study Number 1278600, 2009. – available upon request) tests on mutagenicity (reverse mutation assays) and also on genotoxicity (micronucleus test, chromosome aberration test) remain unmentioned by the assessment report and the monograph. These tests could not detect mutagenic or genotoxic effects of Ginkgo biloba. Two publications are listed in **ANNEX 1 (b)**. Carcinogenicity: a series of test systems have shown an anti-carcinogenic and chemo-preventive activity of *Ginkgo biloba*. They remain unmentioned and are added to the listing attached (**ANNEX 1 (c)**). Genotoxicity and carcinogenicity: the comments on positive effects of "*Ginkgo biloba*" are derived from an NTP report (NTP technical report 578, 2013). The results of this report are not of any relevance: The *Ginkgo biloba* extract used for the study is not conform to a pharmacopoeia or definition of an approved *Ginkgo biloba*. It contains several highly toxic compounds. First the content of alkylphenols including ginkgolic acid was more than double of the allowed (10.45ppm). Second several heavy metals were found, including antimony, arsenic, cadmium, lead, mercury, and molybdenum. Third pesticides could be detected, including carbendazim and 2-polyphenol. Compounds of these 3 groups are well-known for neurotoxic, mutagenic and carcinogenic effects. In addition they influence fertility and have teratogenic effects. Each single impurity would be sufficient to disqualify a compound for the preparation of a medicinal product for the use in human or even animal. Of course toxicological	The assessment report is summarising the data which contribute to establishing a harmonized view in a European Union monograph. It is mentioned in the disclaimer of the draft assessment report supporting the public consultation on the monograph that the focus is not to comment on the assessment report. If suggestions for changes of the monographs are justified and substantiated with references, the suggestions are discussed and if finally endorsed the relevant documents will be amended. With respect to the existing literature it is not the objective to include all publications. If appropriate, specific references were added. The HMPC is aware that the extract used in the NTP study has a different specification but as there are similarities in the spectrum of constituents the data are considered.

Section number and heading	Interested party	Comment and Rationale	Outcome
		investigations with substances containing one, two or all three compounds of this listing may confirm the toxic effects thereof, but they have to remain without implication for a herbal preparation like *Ginkgo biloba* according to the Pharm Eur.	
5.3. Preclinical safety data	Midas Pharma GmbH	We propose to delete the paragraphs on genotoxicity and carcinogenicity: "~~A *G. biloba* extract similar to the monograph relevant extract was tested in a series of studies for genotoxicity and carcinogenicity. It was positive for gene mutation in bacteria and equivocal and negative for chromosome mutations in two separate *in vivo* tests in peripheral erythrocytes and bone marrow cells in mouse.~~ ~~A carcinogenicity study was conducted on a *Ginkgo biloba* extract similar to the monograph relevant extract. Thyroid gland tumours found in a rat carcinogenicity study and hepatocellular carcinoma found in a mouse carcinogenicity study are considered rodent specific, non-genotoxic response associated (with long-term treatment) with high doses of hepatic enzyme inducers. These types of tumours are not considered relevant to humans. Overall, from the carcinogenicity study there is no proof for an increased cancer risk identified at present for patients taking Ginkgo medicinal products at their approved posology.~~" It should be replaced by the following: "Investigations on mutagenicity, genotoxicity and carcinogenicity with preparations according to the relevant extract of the monograph remained negative. In contrast, *Ginkgo biloba* extract has been shown to protect against cancer induction in several models, mainly due to its antioxidative and free radical scavenging properties."	Not endorsed. Due to the variability of herbal preparations evaluation of literature is not restricted to herbal preparations addressed in the final monograph. All relevant data were taken into account. The HMPC is aware that the extract used in the NTP study has a different specification but as there are similarities in the spectrum of constituents the data are considered.

Traditional use

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	IPSEN PHARMA	**We are not in favour of proposing powdered herbal substance as traditional use considering the high content in ginkgolic acids of the leaves.** The content of ginkgolic acids in Ginkgo leaf extracts as required by the European Pharmacopoeia (Ph.Eur.) should not exceed 5 ppm. The toxicity of the Ginkolic acids is clearly highlighted in the draft assessment report on Ginkgo biloba L., folium (refer to pages 39, 40, 43, 45, 48….). A maximum daily dosage of 240 mg EGb extract (WEU) limits the exposure of the patient to 1.2 µg ginkgolic acids per day while the recommended daily dosage of powdered herbal substance in the draft monograph (THMP) is 750 mg which will expose the patient to a high level of ginkgolic acids for which we lack of safety data. The same safety standards to all Ginkgo products should apply irrespective of the use (WEU or THMP).	Not endorsed. If there is a concern about the ginkgolic acid content in a traditional herbal medicinal product this shall be addressed in an individual application if the specification of the Eur. Ph. is not met.
2. Qualitative and quantitative composition	Schwabe	**We disagree with the use of "Powdered herbal substance" as active ingredient of THMP products.** **Rationale** Article 16a (1) e) of directive 2001/83 EG requires that "*in particular the product proves not to be harmful in the specified conditions of use*". According to the GUIDELINE ON THE	Not endorsed. The threshold of 5 ppm was linked to the relevant monograph of the Eur. Ph. and can be regarded as safe. As there was a complex process which led to the definition of this threshold, this does not implicit that

Section number and heading	Interested party	Comment and Rationale	Outcome
		ASSESSMENT OF CLINICAL SAFETY AND EFFICACY IN THE PREPARATION OF COMMUNITY HERBAL MONOGRAPHS…. (EMEA/HMPC/104613/2005), the basic requirements for a THMP encompass that *the product is not harmful under normal conditions of use*. This basic requirement is not met by powdered *Ginkgo biloba* leaves due to its content of harmful constituents. Therefore powdered *Ginkgo biloba* leaves do not qualify for a THMP monograph. Dried Ginkgo leaves contain up to 2% ginkgolic acids (Jaggy and Koch 1997). Ginkgolic acids have been reported to have allergenic, cytotoxic and neurotoxic properties. They were found to be allergenic in vitro and in vivo (Lepoittevin 1989, Hausen 1998, Koch et al. 2000, Sowers et al. 1965; Becker & Skipworth 1975; Jirásek und Brozková 1981; Nakamura 1985; Tomb et al. 1988; Hausen & Vieluf 1997; Chiu et al. 2002). They were embroytoxic in the chick embryo test (Baron-Ruppert and Luepke 2001) and induced cytotoxicity in HaCaT keratinocytes and rhesus monkey kidney tubular cells LLC-MK (Hecker et al. 2002). Further publications reported about cytotoxic and neurotoxic effects (Westendorf & Regan 2000, Ahlemeyer et al. 2001, Liu & Zeng 2009). There is scientific consensus that the content of ginkgolic acids in Ginkgo leaf extracts must be limited to a maximum of 5 ppm: This is a requirement of compendial monographs such as the European Pharmacopoeia (Ph.Eur.), German Pharmacopoeia (DAB) and the USP, as well as in the monographs prepared by independent scientific committees such as the German Commission E or WHO. An EM(E)A guideline (EMEA/MRL/668/99, EWG 2377/90) even restricted the use of homeopathic *Ginkgo biloba* preparations in veterinary medicine to assure that the content of ginkgolic acids in foodstuffs derived from treated animals will not exceed the accepted amounts from human therapy. Taking the maximum daily dosage of 240 mg extract, the <5	reasonable levels above this threshold are necessarily associated with a risk. With respect to traditional use the safety of the herbal preparation is based on long-standing used. There are no specific reports about observations associated with intake of low dosages of powdered Ginkgo biloba leave preparations.

Section number and heading	Interested party	Comment and Rationale	Outcome
		ppm requirement limits the exposure of the patient to 1.2 µg ginkgolic acids per day. In comparison, the recommended daily dosage of powdered ginkgo leaves in the draft monograph is 750 mg which corresponds to an exposure of the patient to up to 15,000 µg ginkgolic acids per day, the 12,500 fold amount compared to extracts. Extracts complying with the Ph.Eur., particularly EGb 761®, have been extensively clinically tested and there is a vast amount of post-marketing experience. For example, the company Schwabe placed 8.7 billion daily dosages of Ginkgo extract EGb 761® on the market between 1989 and 2012. Comparable safety data and post-marketing experience with products containing powdered ginkgo leaves that would allow conclusions to be made about the safety of the use of these products are not available. In the assessment report, the following statements confirm the need for the limitation of the patient's exposure to ginkgolic acids: *"The content of ginkgolic acids is limited with max. 5 ppm. The limit value of 5 ppm was chosen since it complies with the detection limit recordable by routine methods, thus allowing to assure to a maximum degree removal of these compounds from therapeutically used extracts."* (page 5) "*In crude Ginkgo extracts a group of alkylphenols (e.g. ginkgolic acids, ginkgol, bilobol) has been described to exhibit potential contact allergenic and toxic properties. A maximum concentration of 5 ppm has to be maintained to comply with the Ph. Eur. and to ensure safety of use for Ginkgo biloba leaf extracts.*" (page 39) *"The high toxic potential of ginkgolic acids and the following*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		completest possible elimination during manufacturing ginkgo extracts was confirmed in an in vivo study." (page 47/48) The publications of Hecker et al. (2002) and Liu and Zeng (2009) on the cytotoxicity, Ahlemeyer et al., (2001) on the neurotoxicity, and Baron-Ruppert and Luepke (2001) on the embryotoxicity of ginkgolic acids are discussed in the assessment report. (pages 39, 40, 43, 45) Taking the above into consideration, it would appear appropriate to apply the **same safety standards to all Ginkgo products**, independent of their status (well-established use, THMP or veterinary homeopathic) and consequently limit the maximum levels of the daily exposure of the patient to ginkgolic acids (in the range of 1.2 µg).	
2. Qualitative and quantitative composition	Weleda AG	ii) Herbal preparations a) Powdered herbal substance b) Liquid extract from fresh leaves (DER 1:2-3) ; extraction solvent: ethanol 65 % (V/V)	Not endorsed. (see above)
3. Pharmaceutical form	Weleda AG	Herbal preparations in solid or liquid dosage forms for oral use.	Not endorsed. The herbal preparation suggested is not included into the monograph.
4.1. Therapeutic indications	ARKOPHARMA Laboratories	**Comments:** The proposed therapeutic indication for the powdered ginkgo leaf, which only focuses on peripheral circulatory disorders, is partly in line with the approved traditional indications registered in Spain and with a long-standing use of the product as food supplement on the French market. Beside symptoms associated with minor circulatory disorders, the traditional use of the powdered ginkgo leaf in "mild brain deficits of organic origin and behavioral disorders" has also	Not endorsed. It is acknowledged that there is some tradition in the indications mentioned. However, the indications suggested to amend the traditional use are not suitable for traditional herbal medicinal products.

Section number and heading	Interested party	Comment and Rationale	Outcome
		been recognized by Spanish Authorities, since 1990. Additionally, as reported in the draft assessment report (EMA/HMPC/321095/2012, page 14/120), a powdered ginkgo leaf product has been marketed in France for improvement of blood circulation, heavy legs and haemorrhoids, and, also, for vertigo, and memory deficit, since 1984. A second therapeutic indication is fully justified based on the long standing use of powdered ginkgo leaf: Additionally, it is usual to specify that the symptoms defined under the already proposed therapeutic indication are known as "symptoms of Raynaud's syndrome". **It is proposed to read:** "*Traditional herbal medicinal product for the relief of heaviness of legs and the sensation of cold hands and feet associated with minor circulatory disorders (symptoms of Raynaud's syndrome)*". *"Traditional herbal medicinal product for the improvement of memory, concentration and vertigo".*	
4.2. Posology and method of administration	Weleda AG	**Posology** *Adults, elderly* Single dose: 250-360 mg, 100 drops [8]. Daily dose: 250 mg, 200 drops [8].	Not endorsed. The herbal preparation suggested is not included into the monograph.
4.4. Special warnings and precaution for use	ARKOPHARMA Laboratories	**Comments:** The fact to refer systematically to undesirable effects reported for the dry extract (DER 35-67:1) in the case of the traditional use of the powdered ginkgo leaf preparation is questionable from a scientific point of view. Based on highly different content of constituents between the quantified and refined dry extract and the starting material (ginkgo leaf), it looks not relevant to consider that special warnings and precaution for use, interactions with other medicinal products and undesirable effects which may be mentioned for the dry	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		extract (DER 35-67:1) have also to be taken into account for the powdered herbal substance (e.g. the terpene lactone content being 0.06-0.23% ginkgolides A, B, C, J and up to 0.26% bilobalide in the herbal drug, as cited in the draft assessment report, page 4/120, it is 10 to 50 times lower than the terpene lactone content of the quantified and refined dry extract). Meanwhile, although no causal link has been established between the use of powdered ginkgo leaf preparation and antiplatelet treatments, it seems justified and sufficient, as often mentioned in textbooks, to mention the possibility of interactions with anticoagulants (see below under 4.5). **It is proposed to read:** *"The use in children and adolescents under 18 years of age has not been established due to lack of adequate data".* *"If the symptoms worsen during the use of the medical product, a doctor or a qualified healthcare professional should be consulted".* ~~*The following special warnings are based on observations reported for extracts of G. biloba.*~~ ~~*"In patients with a pathologically increased bleeding tendency (haemorrhagic diathesis) and concomitant anticoagulant and antiplatelet treatment, the medicinal product should only be used after consultation with a doctor."*~~ ~~*"Preparations containing Ginkgo might increase susceptibility to bleeding, the medicinal product should be discontinued as a precaution 3 to 4 days prior to surgery".*~~ ~~*" In patients with epilepsy, onset of further seizures – promoted by intake of Ginkgo preparations – cannot be excluded.*~~	

Section number and heading	Interested party	Comment and Rationale	Outcome
		~~*Concomitant use of G. biloba containing products and efavirenz is not recommended (see section 4.5).*~~	
4.5. Interactions with other medical products and other forms of interaction	ARKOPHARMA Laboratories	**Comments:** In accordance with previous comments introduced under "4.4 Special warnings and precaution for use", it looks not justified to include mentioned interactions with other medicinal products. As a general statement, the possible increase of the effects of anticoagulants may be included. **It is proposed to read:** *"Ginkgo leaf may increase the effects of anticoagulants such as coumarin derivatives".*	Endorsed.
4.6. Fertility, pregnancy and lactation	ARKOPHARMA Laboratories	**Comments:** In accordance with previous comments introduced under "4.4 Special warnings and precaution for use", it is proposed to delete all the text and to include the standard comment used under "Traditional use". **It is proposed to read:** *"Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended".* *"No fertility data available".*	Endorsed.
4.8. Undesirable effects	ARKOPHARMA Laboratories	**Comments:** In accordance with previous comments introduced under "4.4 Special warnings and precaution for use" and in absence of undesirable effects observed through the post-marketing surveillance system on the powdered ginkgo leaf since 1990 in Spain, it is proposed to reconsider and simplify the described possible undesirable effects in a more appropriate way.	Partially endorsed. The suggested wording is modified according to the template for European Union monographs.

Section number and heading	Interested party	Comment and Rationale	Outcome
		It is proposed to read: *"Gastrointestinal disorders, headaches and allergic reactions are possible adverse effects".* *"If other adverse reactions not mentioned above occur, a doctor or a qualified healthcare professional should be consulted".*	
5.3. Preclinical safety data	ARKOPHARMA Laboratories	**Comments:** In accordance with previous comments introduced under "4.4 Special warnings and precaution for use", it is proposed to delete all the text and to include the usual standard comment under "Traditional use". **It is proposed to read:** *"Not required as per Article 16c (1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product".* *"Adequate tests on reproductive toxicity and tests on genotoxicity and carcinogenicity have not been performed".*	Endorsed.