



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2012
EMA/HMPC/196894/2012
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Public statement on *Viscum album* L., herba (EMA/HMPC/57109/2011)

Table 1: Organisations and/or individuals that commented on the draft Public Statement on *Viscum album* L., herba as released for public consultation on 15 October 2012 until 15 February 2012.

	Organisations and/or individuals
1	HELIXOR
2	International Association of Anthroposophic Pharmacists (IAAP)
3	International Federation of Anthroposophic Medical Associations (IVAA)
4	Phytolab
5	AESGP



Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Helixor	<p>We appreciate the detailed analyses done by the MLWP on behalf of the HMPC to evaluate the available data on non-clinical and clinical use of <i>Viscum album L.</i> in oncology as well as the information on its regulatory status.</p> <p>Some details presented in the Assessment Report appear to us to be not up to date or incomplete. So we would like to provide you with some supplementary information on some statements within the report as indicated below.</p>	<p>We thank Helixor for the appreciation and additional information regarding the market status of <i>Viscum album</i> preparations in the EU.</p>
IAAP	<p>Dear Sirs,</p> <p>with interest we have studied the HMPC document „Public statement on <i>Viscum album L.</i>, herba“ (EMA/HMPC/57109/2011) which can be commented by stakeholders and public until February 15th 2012 and the Assessment report on <i>Viscum album L.</i>, herba (EMA/HMPC/246778/2009). As you know <i>Viscum album</i> preparations are also widely used in anthroposophic medicine. The IAAP amongst other also takes care about the publication of manufacturing methods of <i>Viscum album</i> preparations (see the template).</p> <p>The IAAP is the governing body within the Medical Section of the School of Spiritual Science of the international community of anthroposophic pharmacists http://www.iaap.org.uk/profil/index.html . The IAAP full members are http://www.iaap.org.uk/profil/organisations.html:</p> <p>The Austrian Association ÖGAPh (Österreichische Gesellschaft anthroposophischer Pharmazeuten - Austrian Society of Anthroposophic Pharmacists); www.oegaph.at The Belgian/Dutch Association BNVAA (Belgisch-Nederlandse Vereniging van Antroposofisch georiënteerde Apothekers - Belgian Dutch Association of AnthroposophicPharmacists);</p>	<p>We thank the IAAP for its appreciation and comments on the assessment report.</p>

	<p>The Brazilian Association Farmantropo (Associação Brasileira de Farmácia Antroposófica - Brazilian Anthroposophic Pharmacy Association); www.farmantropo.com.br</p> <p>The British Association, BAAP (British Association of Anthroposophic Pharmacists) www.baap.info</p> <p>The French Association AFERPA (Association Française d'étude et de recherche sur la pharmacie anthroposofique - French Association for Studies and Research on Anthroposophic Pharmacy);</p> <p>The German Association GAPiD (Gesellschaft Anthroposophischer Apotheker in Deutschland - Society of Anthroposophic Pharmcists in Germany); www.gapid.de</p> <p>The Italian Association SOFAI (Società di farmacisti antroposofi in Italia - Society of Anthroposophic Pharmacists in Italy).</p> <p>The pharmacist section of the Swiss association VAEPS (Verband für Anthroposophisch Erweiterte Pharmazie in der Schweiz - Association for Anthroposophically Extended Pharmacy in Switzerland). www.vaeps.ch</p> <p>Amongst other the IAAP publishes the "Anthroposophic Pharmaceutical Codex" APC which gathers information on pharmaceutical definitions, standards, manufacturing methods, etc and publishes these into the public domain http://www.iaap.org.uk/downloads/codex.pdf</p> <p>Please find our comments attached in the relevant template.</p> <p>We acknowledge your position, i.e. that the evaluation of herbal medicines with <i>Viscum album</i> with respect to the well established use is not possible because some essential criteria for evaluation are not fulfilled. We as a stakeholder are further working to provide relevant pharmaceutical information on the manufacturing of <i>Viscum album</i> preparations to the public domain. We wish to point out, that the ultimate details of production (e.g. precise dedicated equipment, batch size etc.) are not available to the IAAP, but will stay with the concerning pharmaceutical enterprise, until the information is requested by a competent authority.</p>	
IVAA	<p>The IVAA (International Federation of Anthroposophic Medical Associations) represents and coordinates the national anthroposophic doctors' associations on both the European and international levels in regard to political and legal affairs. As a corporate body the IVAA functions as the umbrella organisation for the national anthroposophic doctors' associations</p>	<p>We thank the IVAA for its appreciation and its understanding of the position of the HMPC and its tasks within the framework of Directive 2004/24/EC amending</p>

	<p>worldwide in regard to political and legal concerns (EU COM Transparency Register ID number: 60399267990-31)</p> <p>IVAA very much appreciates the efforts of HMPC to evaluate the situation of <i>Viscum album</i> in oncology in terms of use, regulatory status and availability of non-clinical and clinical data. As mistletoe preparations are an essential part of the integrative medical approach which anthroposophic medicine provides to the treatment of cancer, we regret that a well-established use monograph could not be drafted.</p> <p>Nevertheless, we are very grateful for the publication of the draft Public Statement, Assessment Report, and List of References in line with the procedure EMA/HMPC/84530/2010, with the possibility to give comments during a public consultation, supporting the assessment of <i>Viscum album</i> L., herba.</p> <p>The work done by the HMPC is very important, having in mind the fact that mistletoe preparations are the most frequently used complementary and alternative methods to treat cancer in German-speaking countries (Horneber et al. 2008). Mistletoe preparations are an essential part of the integrative approach to oncology in specialised hospitals in Germany, Switzerland, Sweden and the United Kingdom. In addition, mistletoe preparations are used by more than 15.000 physicians in Europe for the treatment of cancer in outpatient settings in 22 EU Member states, Norway and Switzerland.</p> <p>The legislative and regulatory situation for <i>Viscum album</i> L., herba preparations used in oncology varies remarkable between EU Member states. This variation has negative impact on the availability of these medical products in the different member states. It causes inequality for patients who want to use <i>Viscum album</i> L preparations for the treatment of their cancer. A monograph could have contributed to a harmonisation of the common market in the EU for these medicinal products. IVAA regrets that this has not been achieved.</p>	<p>Directive 2001/83/EC.</p>
<p>Phytolab</p>	<p>In its draft public statement on <i>Viscum album</i> L. herba the HMPC concludes on the use of <i>Viscum album</i> in cardiovascular indications:</p> <p><i>"... that cardiovascular disorders for which traditional herbal preparations of Viscum album are used, are not considered suitable for self medication."</i></p> <p>Based on its long standing traditional use in the supportive and p</p>	<p>Despite the long standing traditional use of <i>Viscum album</i> preparations for mild cardiovascular conditions, a herbal monograph for conditions like mild hypertension is considered not to be in accordance with the Directive 2004/24 (EC).</p>

	<p>rophyactic treatment of cardiovascular complaints it can clearly be stated that <i>Viscum album</i> preparations, predominantly the infusion, the powdered herb and an ethanol-stabilised pressed juice prepared from the fresh herb (Intractum Visci 1:1, ethanol content 52 – 62 % V/V) as well as the pressed juice from the fresh herb clearly fulfill the tradition criterion of min 15/30 years of traditional medicinal use set forth in Directive 2004/24(EC).</p> <p>As documented in the literature (see below) this history of medicinal use can be traced back until at least 1934 (BRITISH PHARMACEUTICAL CODEX 1934). Keeping in mind that throughout much of this time there have been practically no effective/safe alternative treatments for hypertensive patients besides <i>Rauwolfia</i>, the importance of <i>Viscum album</i> preparations for many of that time period is remarkable. However, it has been well recognized that the pharmacological effects were more of a modulative nature, affecting the general well being of patients rather than having a pronounced antihypertensive effect per se (WEISS 1974).</p> <p>The major argument in the draft opinion against establishing a monograph on the traditional use of <i>Viscum album</i> is the consideration that the kind of cardiovascular disorders for which traditional herbal preparations of <i>Viscum</i> have been used for so long <i>“are not considered suitable for self medication.”</i> This is not easily understandable in view of the fact that an HMPC monograph has recently been finalized on <i>Leonurus cardiaca</i> L., herba which stipulates as a therapeutic indication <i>“THMP used to relieve symptoms of nervous <u>cardiac complaints</u> such as palpitations, after serious conditions have been excluded by a medical doctor.”</i></p> <p>The example of <i>Leonurus cardiaca</i>, as well as the one of <i>Tanacetum parthenium</i> rightly reflects the view of the European Commission that <i>“community herbal monographs with indications relating to traditional use may refer to a prior medical diagnosis intended to prevent treatment of more serious pathologies with traditional herbal medicinal products.”</i></p> <p>If, in the case of <i>Viscum album</i>, the HMPC considers the indication of mild hypertension as being too serious of nature it would be welcome if a conclusive argumentation would be</p>	<p>The HMPC considered that the data and discussion leading to the monograph on <i>Leonurus cardiaca</i> were different. Generally the HMPC draws the conclusion that a herbal monograph for conditions like mild hypertension is considered not to be in accordance with the Directive 2004/24/EC.”</p>
--	--	--

	<p>provided why this is seen in that way.</p> <p>Worth of note, in its recently published "<i>Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health</i>" (EFSA 2011) the European Food Safety Authority has recently documented its view that health claims on the reduction of blood pressure are considered to reflect a beneficial physiological effect and conclusively food products claiming to reduce blood pressure are considered sufficiently safe since no food is designated to be used under medical supervision only!</p> <p>If the HMPC does not see a possibility to modify its opinion that any reference to "blood pressure" or "hypertension" would not be acceptable, there are several possible indications which could be considered nevertheless:</p> <p>In analogy to <i>Leonurus cardiaca</i> viscum has also been used for nervous cardiac complaints (Berger 1950, British Herbal Pharmacopoeia 1976, Valnet 2001, Potter 2003).</p> <p>Through many decades, Viscum preparations have been used for the prevention of arteriosclerosis. Generally, Viscum preparations are perceived by elderly people (and have been used and recommended in phytotherapy) as a mild treatment to prevent a decline in the performance and functionality of the heart and circulatory system. Keeping in mind the stipulations of R. F. Weiss (1974) regarding the effects on the general well being of hypertonic patients this is well understandable and has been reflected in the indication according to § 109 a German Drug Law as of 1995 indicating the traditional use of mistletoe preparations for the support of cardiovascular function.</p> <p>If the term "cardio" was considered a "no-go" (which would be difficult to understand anyway in view of the Leonurus indication!) the possibility would still be left to refer to vascular function and nervous heart complaints exclusively.</p> <p>Possible indications for Viscum preparations sufficiently reflecting the well documented</p>	
--	--	--

	<p>traditional knowledge and available pharmacological data could be, e.g.:</p> <p>“Traditional Herbal Medicinal Product used for the prevention of age related arteriosclerosis (alternatively: (cardio)vascular impairment)”</p> <p>and/or</p> <p>“Traditional Herbal Medicinal Product used to relieve symptoms of nervous cardiac complaints after serious conditions have been ruled out by a doctor”</p> <p>Conclusion In view of the very long tradition of medicinal use of <i>Viscum album</i> preparations, the variety of its traditionally documented cardiovascular indications and the prominent presence of <i>Viscum album</i> preparations on various large national markets in the EU it would appear inappropriate not to establish a traditional monograph on <i>Viscum album</i> herba preparations. Even more so and in particular in relation to recent developments in the food area.</p>	<p>The option for a public statement instead of a monograph for <i>Viscum album</i> has been extensively discussed within the MLWP and the HMPC. Finally, a herbal monograph for conditions like mild hypertension is considered not to be in accordance with the Directive 2004/24/EC.”</p>
--	---	--

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
	AESGP	<p><u>Draft public statement:</u></p> <p>We do not agree with the statement “that cardiovascular disorders for which traditional herbal preparations of <i>Viscum album</i> L., herba are used are not considered suitable for self medication”.</p> <p>Mistletoe is one of the herbal medicinal products listed in annex 1c of the German legal act for pharmacy-only resp. non-prescription medicine [1], which</p>	<p>The option for a public statement instead of a monograph for <i>Viscum album</i> has been extensively discussed within the MLWP and the HMPC. Finally, a herbal monograph for conditions like mild hypertension is considered not to be in accordance with the Directive 2004/24/EC.”</p>

		<p>regulates the access to medicinal products for which no prescription is required and no pharmacist needs to be involved in selling (equivalent to the British general sale list). These herbals are used only to relieve symptoms and minor complaints, have a positive benefit-risk ratio and fulfil the demands of a herbal drug with documented long-term use and a high level of safety, a self medication is allowed.</p> <p>Since 30 June 2011 ten traditional-use-registrations for mistletoe in monocomponent products were granted [2]. Among them, a traditional German preparation (Bad Heilbrunner Misteltee) may serve as an example with the indication “to support cardiovascular functions” [3]. Consequently the German Federal Institute for Drugs and Medical Devices (BfArM) has verified that the comminuted herbal substance of mistletoe as herbal tea for oral use has a recognised efficacy and an acceptable level of safety according Article 10a of Directive 2001/83/EC. The requirement laid down in Article 16a(1)(d) of Directive 2001/83/EC concerning the period of traditional use as laid down on Article 16c(1)(c) is fulfilled.</p> <p>We are of the opinion that traditional herbal preparations of <i>Viscum album</i> L., herba for oral intake can be considered suitable for self medication in cardiovascular disorders with the following indication “Traditional herbal medicinal product used to support cardiovascular functions. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use”.</p> <p>Should this not be accepted, we could suggest adding “after initial diagnosis by a doctor” or “after serious conditions have been excluded by a medical doctor”. Cardiovascular symptoms can fall in the remit of collaborative care i.e. be self-managed after an initial diagnosis by a doctor has cleared any possible underlying serious cause and/or pathology requiring doctor`s supervision. This approach is in line with the final HMPC monograph on <i>Leonurus cardiaca</i>, L., herba (EMA/HMPC/127428/2010).</p>	
--	--	---	--

		<p>With regard to the first conclusion of the draft Public statement on the use of <i>Viscum album</i> in cancer therapy, we would like to point out that this lies only outside the scope of chapter 2a (specific provisions applicable to traditional herbal medicinal products) of Directive 2001/83/EC. The current statement may otherwise be misinterpreted. Such a public statement shall not be understood as a negative assessment of the herbal substance and preparations thereof, as it may be possible that applicants can submit the data or information identified by the HMPC as missing for the purpose of preparing a monograph in dossiers for national marketing authorisations.</p>	<p>The public statement specifies that the requirements are not fulfilled: ... requirement laid down in Article 16a(1)(a) of Directive 2001/83/EC that the indications are “exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment”.</p>
--	--	--	--

SPECIFIC COMMENTS ON TEXT: ASSESSMENT REPORT

Section number and heading	Interested party	Comment and Rationale	Outcome
Draft assessment report GENERAL	AESGP	<p>The work done by the HMPC is very important having in mind the fact that mistletoe preparations are the most frequently used complementary and alternative methods to treat cancer in German-speaking countries (Horneber et al. 2008). In France they are the second most used complementary therapy for cancer treatment (Prof. Simon Schraub – Université de Strasbourg – Conférence Médecines non-conventionnelles et Cancers – Bruxelles 16 Décembre 2011). Figures from other Member States are not available but large use is noted among others in Italy, the United Kingdom, Belgium, Sweden and some CEEC countries. Also the use in specialised hospitals in Germany, Switzerland, Sweden and the United Kingdom is known.</p>	<p>The additional information by AESGP is welcomed. For further implementation in the assessment report: see separate heading underneath</p>

		<p>We take note of the fact that the assessors restricted themselves to literature published between 2006 and 2010 and did not consider literature with the outcome criterion immuno-modulation and excluded studies only describing immunologic parameters.</p> <p>Marketing authorisations have been granted with <i>Viscum album</i> in Europe; it would be interesting to know their date of authorisation and legal basis In addition we have been informed that a monograph dealing with manufacturing methods used also for the production of <i>Viscum album</i> preparations for parenteral use is currently drafted by the International Association of Anthroposophic Pharmacists (IAAP) to be published in the next revised edition 3.0 of the Anthroposophic Pharmaceutical Codex (APC) in 2012. Furthermore, we have heard that the outdated <i>Visci albi herba recens</i> monograph in the Hager´s Encyclopaedia will be revised thoroughly in 2012. Even though the date of the last update shows currently 25.02.2011, the content of this monograph has not been revised since several years as can be seen from the publication dates of the literature (newest is from 1993, most publications are from the 70ies and 80ies).</p> <p>As the development in the <i>Viscum album</i> area continues at high speed some data in the report are already outdated and some may not be up to date any more very soon. We have amended the draft Assessment Report in line with the information we could find in this respect. This mainly concerns historical data, the regulatory status, information on the use and indications and some toxicological and clinical data. With regard to non-clinical and clinical data available in the public domain and having in mind ongoing scientific research on <i>Viscum album</i> as well as the announced publication/revision of the above mentioned monographs, review of the Assessment Report/re-consideration of establishment of a mistletoe monograph should be reconsidered in the near future.</p>	
Draft assessment report	AESGP	It is critical that the draft assessment report be amended as the draft	The assessment report was accompanied

GENERAL		<p>was unfortunately wrongly used by a competent authority outside the EU to deny a clinical trial application for a mistletoe-containing product with reference to the draft public statement on <i>Viscum album</i> L., <i>herba</i> and draft assessment report. The authority justified its decision referring to the “EMA documentation” where it says that there are not sufficient toxicology studies for mistletoe products available so that they could not grant approval for the clinical study.</p>	<p>by a statement indicating the intention and the status of being a draft (see disclaimer on page 1 draft AR). This draft AR supported a draft public statement that gives the reasons why a monograph cannot be established according to the specific tasks of the HMPC within Directive 2001/83/EC as amended.</p>
<p>Introduction (page 1 of the draft AR)</p>	AESGP	<p>Herbal preparations: Host tree fir (A) is missing (e.g. Helixor A). Host trees maple (Aceris), almond (Amygdali), birch (Betulae), hawthorn (Crataegi), or ash (Fraxini) are missing (e.g. abnobaVISCUM preparations).</p> <p>Please modify as follows: Differing in terms of the manufacturing process: Fermented and unfermented aqueous extracts from leaves, stems, blossoms, sinkers and/or berries are used. Hosts can be apple tree (M), oak (Qu), pine (P), ø elm (U), fir (A), maple (Aceris), almond (Amygdali), birch (Betulae), hawthorn (Crataegi), or ash (Fraxini) [used in oncology]. The types of herbal preparations listed are expressed juice, ethanol extracts, wine extracts, aqueous extracts, tinctures and dry extracts [used in cardiovascular disorders].</p> <p>Pharmaceutical forms: Abnobaviscum preparations are also authorized for intravenous administration hence the sentence should read: “Herbal preparations in solid or liquid dosage forms for oral use and liquid dosage forms for subcutaneous and intravenous injection.”</p>	<p>The missing tree species are added now.</p> <p>Pharmaceutical form: intravenous is added.</p>

AR Page 1, 2 nd line	Helixor	Page 1, 2nd line in table, right column first bullet: To the list of host trees the fir (<i>Abies alba</i> L.) should be added. Mistletoes grown on fir trees are used as raw material for HELIXOR® A.	Information is added.
TOC (page 2)	AESGP	Should the title 1.2 Information about the products on the European market remain as such or be changed to read 'information about products on the market in the Member States' to be consistent with the template.	Correction is made.
AR Page 3, last sentence 1 st paragraph	Helixor	Page 3, Herbal substance(s), last sentence of the first paragraph: In this case the fir is mentioned but the pine is missing.	Information is added.
1.2 information about the products on the European market (page 6)	AESGP	The authorization dates for Germany are not correct. They should read: ABNOBAVISCUM (oldest references dates from 1985) [...] Iscador (oldest reference dates from 1978).	Correction is made.
AR Page 6, 1 st paragraph	Helixor	Page 6, first paragraph: the origin of the statement .In Germany, there are 127 authorised single active ingredient products. is not clear. At present, 5 different mistletoe product lines (abnobaVISCUM®, HELIXOR®, Iscador®, Iscucin®, and Lektinol®) have marketing authorisations in Germany. Cefalektin®, Eurixor®, and Isorel® have lost marketing authorisation in Germany and/or are produced no longer. 4 out of 5 manufacturers offer products at different strengths from mistletoes grown on different host trees as detailed below: abnobaVISCUM®: 72 separate products with marketing authorisation - from 9 different host trees (abnobaVISCUM® Abietis, abnobaVISCUM® Aceris, abnobaVISCUM® Amygdali, abnobaVISCUM® Betulae, abnobaVISCUM® Crataegi, abnobaVISCUM® Fraxini, abnobaVISCUM® Mali, abnobaVISCUM® Pini, abnobaVISCUM® Quercus) and at 8 different strengths each (20mg, 2mg, 0.2mg, 0.02mg, D6, D10, D20, D30).	Information is added.

		<p>HELIXOR®: 27 separate products with marketing authorisation</p> <ul style="list-style-type: none"> - from 3 different host trees (HELIXOR® M, HELIXOR® P, HELIXOR® A) and at 9 different strengths each (100mg, 50mg, 30mg, 20mg, 10mg, 5mg, 1mg, 0.1mg, 0.01mg). <p>Iscador®: 63 separate products with marketing authorisation</p> <ul style="list-style-type: none"> - from 3 different host trees (Iscador® M, Iscador® P, Iscador® Qu) and at 7 different strengths each (20mg, 10mg, 1mg, 0.1mg, 0.01mg, 0.001mg, 0.0001mg) - from 4 different host trees supplemented with metals in very high potencies (Iscador® M c Arg., Iscador® M c Cu, Iscador® M c Hg, Iscador® P c Hg, Iscador® Qu c Arg., Iscador® Qu c Cu, Iscador® Qu c Hg, Iscador® U c Hg) and at 5 different strengths each (20mg, 10mg, 1mg, 0.1mg, 0.01mg) - from 2 different host trees but produced according to a specialized protocol (Iscador® M 5mg spezial, Iscador® Qu 5mg spezial). <p>Iscucin®: 8 separate products with marketing authorisation</p> <ul style="list-style-type: none"> - from 8 different host trees (Iscucin® Abietis, Iscucin® Betulae, Iscucin® Crataegi, Iscucin® Mali, Iscucin® Pini, Iscucin® Populi, Iscucin® Quercus, Iscucin® Tiliae). While all Iscucin® products are available at 8 different homeopathic dilutions, respectively, all potencies of one product line (mistletoe host tree) are registered with the same registration number. <p>So, a total of 171 authorised single active ingredient products are actually available in Germany.</p>	
Regulatory status overview (page 6-7)	AESGP	For Germany and Poland, the box "MA" should be ticked (and 'not known' deleted for Poland). The box "other – specify" should also be ticked for the UK.	Corrections are made, but for the UK no information is transferred.
Page 6, Regulatory status overview:	Helixor	<ul style="list-style-type: none"> - Germany: MA should be ticked. - Latvia: MA should be ticked and .not known. deleted in last column. (HELIXOR® A, M, and P are authorised in Latvia). 	Information is added.
Page 9, Inclusion	Helixor	Why was a time period of only 5 years (2006-2010) used as an inclusion	The period of 2006 – 2011 was chosen

<p>Criteria, first criterion</p>		<p>criterion? One of the prerequisites to establish a well-established medicinal use is that the period of time from the first systematic and documented use of that substance as a medicinal product in the European Community must be not be less than one decade. Quite a number of clinical trials and reviews on mistletoe products published between 2001 and 2005 or before are available, easily accessible for example via the IFAEMM-data base. Additionally, several clinical studies and reviews already enclosed in the .list of references supporting the assessment of <i>Viscum album</i> L., herba. were published earlier than 2006. Therefore, an expansion of the time frame used as inclusion criterion would be consistant with a well-established use monograph.</p>	<p>for the most recent literature search. For publications < 2006 review articles and standard books were used: e.g. Keller et al. (1994), Kienle & Kiene (2003), Horneber (2008), Lange-Lindberg (2006).</p> <p>No further details are included in this assessment report, as they are related to an oncological use of <i>Viscum</i> and this use falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products. The evaluation with respect to well-established use is currently not possible because some essential criteria for evaluation are not fulfilled.</p>
<p>2.1 Information on period of medicinal use in the Community (page 10)</p>	<p>AESGP</p>	<p>Please amend as follows: “ [...] this medicinal approach is rooted in philosophy which considers disease not as an isolated process but sees it rather as part of the human existence and development. [...]” By using substances from nature as a cure for humans, anthroposophical medicine tries to re-establish harmony in the human organisation and expel the disease.</p>	<p>The sentences are corrected.</p>
<p>2.2. Information on traditional/current indications and specified substances/preparations (page 10)</p>	<p>AESGP</p>	<p>- For Austria: oncologic indication is missing: „Unterstützend zu allgemeinen Maßnahmen zur Verbesserung der Lebensqualität bei soliden Tumoren während und nach einer Standardtherapie.“ (“Supportive to general measures in order to improve quality of life in case of solid tumours during and after standard therapy.”).</p> <p>- Germany: In Rote Liste 2010 the following indication is given: “...Anregung von Form- u. Integrationskräften zur Auflösung u.</p>	<p>The suggested information is added.</p>

		<p>Wiedereingliederung verselbständigter Wachstumsprozesse, z. B. bösart. u. gutart. Geschwulsterkrank.; bösart. Erkrank. u. begleitende Stör. der blutbildenden Organe, Anregung der Knochenmarkstätigkeit; Vorbeugung gg. Geschwulstrezidive; definierte Präkanzerosen.“ As you may know this indication will change soon. The new indication is: „... Anregung von Form- und Integrationskräften zur Auflösung und Wiedereingliederung verselbständigter Wachstumsprozesse, z.B. bei bösartigen Geschwulstkrankheiten, auch mit begleitenden Störungen der blutbildenden Organe; bei gutartigen Geschwulstkrankheiten; bei definierten Präkanzerosen; zur Rezidivprophylaxe nach Geschwulstoperationen.“</p> <p>- Poland: oncologic indication is missing : “Zgodnie z antropozoficzną wiedzą o człowieku i przyrodzie Iscador® M/P/Qu jest stosowany w celu zahamowania procesów rozrostu w złośliwych chorobach nowotworowych, schorzeniach układu krwiotwórczego o charakterze złośliwym, do pobudzenia czynności szpiku kostnego, zapobieganiu nawrotom nowotworów oraz w zdefiniowanych pierwszych fazach choroby nowotworowej (stany przedrakowe).” („Iscador® M/P/Qu, solution for injections, is an anthroposophic medicine. According to anthroposophic knowledge of man and nature, Iscador® M/P/Qu is used to slow proliferation processes in malignant tumour diseases and haemopoietic system afflictions of a malignant nature, to stimulate bone marrow activity, to prevent recurrences of neoplasms and in established first phases of neoplastic disease (precancerous states).“)</p>	
2.3 Specified strength/posology/route of administration/duration of use for relevant preparations and	AESGP	<p>We wonder why reference is made here to both the Rote Liste from 2010 and 2011? If so, shouldn't this also be done in Table 2 as well? We would rather recommend including a table as was done for the cardiovascular indications as follows:</p>	<p>The Rote Liste is no longer mentioned. The information is taken to the subheading Germany.</p>

indications		CODE	PHARMACEUTICAL FORM	POSOLOGY	
		Iscador -> codify	Solution for injection	2-3 x weekly 1 ml, in special cases 1 x daily 1 ml	
		Helixor -> codify	Solution for injection	2-3 x weekly 1 ml, in special cases 1 x daily 1 ml	
		Iscucin -> codify	Solution for injection	2-3 x weekly 1 ml	
		Abnobaviscum -> codify	Solution for injection	2-3 x weekly 1 ml	
Page 10, 2.2 Information on traditional/current indications and specified substances/preparations,	Helixor	Table 2: Austria: oncologic indication of HELIXOR® is missing: .Unterstützend zu allgemeinen Maßnahmen zur Verbesserung der Lebensqualität bei soliden Tumoren während und nach einer Standardtherapie (Supportive to general measures in order to improve quality of life in case of solid tumours during and after standard therapy..). Lithuania: oncologic indication is incorrect: .Papildoma gydymo priemonė sergant piktybinėmis ligomis, gyvybingumui ir ligos eigai pagerinti (Complementary therapy in malignant diseases for the improvement of quality of life and possibly the course of the disease).. No entry to Latvia: HELIXOR® has marketing authorisation there. The oncologic indication is .HELIXOR® ir antroposofiskas zāles. Tās ir augu izcelsmes zāles, kuras lieto kā papildterapiju pie ļaundabīgām (malignām) saslimšanām (HELIXOR® is an anthroposophic herbal medicine for the adjunctive therapy in malignant disease)..			Indications in English are taken to the assessment report and the existing texts are omitted or corrected.
3. Non-clinical data	AESGP	We refer to our comments above on the search criteria			See earlier.
3.1 Overview of... & Assessor´s overall	AESGP	Oncology: A reason for not further commenting on these investigations is missing for the category of well-established use products. We would			Sentences adapted.

conclusions on pharmacology		<p>therefore recommend adding the following text: "The spectrum of active <i>Viscum album</i> constituents is broad. Kienle & Kiene (2003) and Tabiasco <i>et al.</i> (2002) report on cytotoxic and immunomodulatory properties of lectins and viscotoxins. These investigations are not further commented as the oncological use of <i>Viscum</i> falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."</p> <p>Oncology: Mechanisms related to adjuvant activity in cancer treatment were investigated but are not further evaluated as oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3).</p>	
3.3 Overview of the available toxicological data regarding the herbal substance(s)/ herbal preparation(s) and constituents thereof	AESGP	<p>The statement reading that 'preclinical toxicological data are limited' is not correct, nor the fact that they are not related to the preparations used in humans. It seems that incomplete information has been reproduced here. The complete table by Kienle and Kiene, 2003 (page 605) is enclosed including the studies referring to Iscador:</p>	<p>The existing table is replaced by the table as published by Kienle en Kiene (2003).</p> <p>Typing error agglutinating has been corrected.</p> <p>The changes suggested under the subheadings of oncology and the overall conclusions have been taken into consideration.</p>

Tab. 123 LD₅₀ von Mistelextrakten, Mistellektinen, Viscotoxinen und Polysacchariden.

	LD ₅₀	
Mistelextrakt (Iscador M)	700 mg/kgKG CD-1 Albinomaus, i.p. ²³²⁸	276 mg/kgKG Swiss Maus, i.p. ²⁴
	348 mg/kgKG C57/BL6-Mäuse, i.p. ²³²⁸	168 mg Frischpflanze/kgKG Maus Applikationsweg unklar ¹⁰⁹⁰
	378 mg/kgKG Sprague-Dawley Ratten, i.p. ²³²⁸	
Mistelextrakt (Iscador Q)	500 mg/kgKG Maus, i.v. ¹⁷⁸²	1200 mg/kgKG Maus, s.c. ¹⁷⁸²
Mistelpflanzensaft	±32 mg/kgKG Maus, i.p. ²⁶¹	
ML I	28,6 Mg/kgKG Maus, Applikationsweg unklar ¹⁷⁷⁸	28 Mg/kgKG Maus, i.p. ⁸¹
ML II	46,7 Mg(VAII)/kgKG Maus, Applikationsweg unklar ¹⁷⁷⁸	1,5 Mg/kgKG Maus, i.p.
ML III		55 Mg/kgKG Maus, i.p.
Viscotoxine	0,5 mg/kgKG Maus, i.p. ¹⁷⁷⁸	Viscotoxine LD ₅₀ 0,1 mg/kgKG i.v. ¹⁷⁷⁸
Polysaccharid- fraktion	> 2,25 g/kgKG Maus, i.p. ²⁶¹	

As this table is limited to the mentioning of marketed final herbal preparations it is not taken to the assessment report.

The following preclinical toxicity evaluations have also been performed with preparations used in humans and have been submitted but have not been considered. We therefore recommend deleting the sentence: "Preclinical toxicological data are limited."

Table 1: Toxicology Programme

Study type and duration	Route of administration	Species	Compound administered	Reference

Single-dose toxicity				
Single-dose toxicity	i.p.	Mouse	Iscador® Qu	Study No. TIF 504
Single-dose toxicity	p.o., s.c., i.p., i.v., i.m	Mouse	Iscador® M and Qu	Nienhaus & Leroi 1970
Single-dose toxicity	i.p.	Rat / Mouse	Iscador® M	Rentea et al. 1981
Single-dose toxicity	s.c.	Rat	Iscador® M special	Study No. 22470
Single-dose toxicity	s.c.	Rat	Iscador® Qu special	Study No. 21190
Single-dose toxicity	s.c.	Rat	Iscador® P	Study No. 22460
Single-dose toxicity	i.v.	Rat	Lektinol®	Mengs 1998
Repeat-dose toxicity				
not indicated	i.v. and i.p.	Mouse	Iscador® M and Qu	Nienhaus & Leroi 1970
1 month	i.v.	Rat	Lektinol®	Mengs 1998
3 months	i.v.	Mouse	Eurixor®	Staak et al. 1997
Genotoxicity				
Ames test	<i>in vitro</i>	-	Iscador® M special	Study No. 22490
Ames test	<i>in vitro</i>	-	Iscador® Qu special	Study No. 21200
Ames test	<i>in vitro</i>	-	Iscador® P	Study No. 22480
Several tests	<i>in vitro</i>	-	Lektinol®	Mengs et al. 1997

Chromosome aberration test	<i>in vitro</i>	-	Iscador® M special	Study No. 31610
Chromosome aberration test	<i>in vitro</i>	-	Iscador® Qu special	Study No. 31620
Micronucleus test	s.c.	Rat	Iscador® Qu special	Study No. PT02-0397
Micronucleus test	s.c.	Rat	Iscador® P	Study No. PT02-0396
Reproductive toxicity				
Fertility	i.p.	Mice	Iscador® Qu	Study No. TIF 504
Teratogenicity	s.c.	Rat	Iscador® Qu special	Ghelman 2003
Teratogenicity	s.c.	Rabbit	Iscador® M special	Study No. 22580
<p>Please, correct typo: ...haemagglutinating...</p> <p>- Acute toxicity - Oncology (page 15): The sentence needs to be completed as follows: " There are limited investigations on short-term toxicity of particular oncological preparations (Maldacker 2006). No further details are given as oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."</p> <p>- Chronic toxicity:</p>				

	<p>Instead of writing “unknown”, we recommend here to also subdivide the section into Cardiovascular and Oncology and add the following sentence under Oncology: Data on chronic toxicity are limited. No further details are given as oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria are not fulfilled (see section 4.3). unknown</p> <p>This sentence would reflect the following studies:</p> <p>Nienhaus & Leroi (1970) observed a marked increase in the weight of thymus and spleen in Varese mice at dose levels of about 5 – 10% of the LD₅₀ of Iscador® M or Qu administered intravenously or intraperitoneally. Higher dose levels caused a reduction of the weight of these organs. Clinical signs of toxicity were mainly tonic-clonic convulsions (no further details reported).</p> <p>Staak and colleagues (1997) determined the effects of repeated administration of a commercial mistletoe extract with standardized lectin content (Eurixor®) on the histological appearance of lung and liver in BALB/c mice. Groups of 5 mice (3 or 8 weeks old) were given the extract at a dose level corresponding to 1 ng lectin/kg bw twice weekly for three months. Thereafter the animals were sacrificed, and lung and liver evaluated histologically. Livers of 3 weeks old mice showed a distinct hyperaemia and an enrichment of leukocytes in blood vessels and perivascular tissue. No fibrotic changes were observed. In 8 week old mice, only hyperaemia without any other changes was detected. In the lungs of 3 week old mice, marked hyperaemia together with mild inflammation occurred, whereas the lungs of 8 week old mice exerted only hyperaemia. No fibrotic changes were seen. In summary, the histological changes caused by the treatment with mistletoe extract represented mainly reversible hyperaemia with partly minimal and reversible signs of inflammation. No organ damage was observed.</p>	
--	--	--

	<p>Mengs (1998) administered an aqueous mistletoe extract (1:1.1 – 1:1.5), the active ingredient of the commercial preparation Lektinol[®], intravenously to rats at dose levels of 0, 0.2, 1.5, or 5.0 mg/kg bw daily for four weeks (5.0 mg/kg bw corresponding to 1.0 µg/kg bw mistletoe lectin). The following parameters were examined: food consumption, body weight gain, clinical signs, ophthalmoscopy, haematology, urine analysis, necropsy, organ weight, and microscopic pathology. No signs of drug-related effects were seen in any determinations. The no observed effect level (NOEL) as well as the no observed adverse effect level (NOAEL) were above the highest dose of 5.0 mg/kg bw given in this study.</p> <p>Genotoxicity ONCOLOGY (page 15): Please complete sentence as follows: “Specific oncological preparations were tested for mutagenic effects in the Ames test and a micronucleus test (Maldacker 2006), and also for chromosomal damage (Kienle & Kiene 2003). No further details are given as oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3).”</p> <p>Reproduction ONCOLOGY (page 16): Please complete sentence as follows: “The effects of specific oncological preparations on pregnancy and embryo-foetal development were investigated (Maldacker 2006). No further details are reported here because oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some</p>	<p>The text of the conclusions is adapted.</p>
--	---	--

		<p>essential criteria for evaluation are not fulfilled (see section 4.3)."</p> <p>Assessor's overall conclusions on toxicology (page 16)</p> <p>Please, delete 2nd sentence as the preparations tested are not different from the ones used in therapeutic conditions (see Table 1 and Maldacker 2006).</p> <p>In animal tests toxicity of <i>Viscum album</i> extracts was assessed as very low. But the preparations tested are different from the ones used in therapeutic conditions. No serious events were observed after oral ingestion. No further comment is given on the results emerging from the investigation of oncological preparations because oncological treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3).</p>	
3.4 overall conclusions on non-clinical data	AESGP	<p>ONCOLOGY:</p> <p>Please complete sentence (we refer to our comments above).</p> <p>Different <i>Viscum</i> preparations have been tested in experimental <i>in vitro</i> as well as <i>in vivo</i> models. No further details are given as the subcutaneous use of <i>Viscum</i> preparations in cancer treatment falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3).</p>	The sentence suggested in bold is added to the overall conclusions.
4.1.2. Overview of pharmaco-kinetic data	AESGP	<p>ONCOLOGY (page 17):</p> <p>This sentence is wrong:</p> <p>"Schöffski <i>et al.</i> (2004; 2005) and Huber <i>et al.</i> (2010) did a pharmacokinetic evaluation on recombinant <i>Viscum</i> lectin analogues. Huber <i>et al.</i> (2010) did a human pharmacokinetic investigation with a <u>complete plant extract</u>. Please correct.</p> <p>Please complete sentence (reason see above):</p> <p>No further details are included in this assessment report, as they are</p>	<p>Huber <i>et al.</i> (2010) is corrected.</p> <p>The sentence in bold is added to the overview of pharmacokinetic data.</p>

		related to an oncological use of <i>Viscum</i> and this use falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."	
4.2.2. Clinical studies	AESGP	ONCOLOGY (page 18): Only the health technology assessment of <i>Viscum album</i> (Lange-Lindberg et al. 2006) is mentioned here, even though many other important reviews exist, see Table 2 in Appendix at the end of this document for further important ones. Please complete sentence (reason see above) and correct typo: "Convincing blinded randomised controlled <u>tr</u> ials are difficult to perform and the therapeutic practice falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."	Additional references are mentioned under 4.2.2. No further details are given on the content of these references, as the assessment report is meant to be limited to general information on the use of <i>Viscum</i> in oncology.
4.2.3. clinical studies in special populations (page 18)	AESGP	Please complete the sentence (reasons stated above): "Chernyshov <i>et al.</i> (1997, 2000) conducted non-randomized placebo-controlled trials in children suffering from respiratory deficiency. These studies are not further commented upon as they fall outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."	The indicated sentence is added.
4.3 Overall conclusions on clinical pharmacology and efficacy (page 18)	AESGP	A supplement (2.1) to the 2nd edition of the Anthroposophic Pharmaceutical Codex will be published in spring 2012 by the International Association of Anthroposophic Pharmacists (IAAP) (http://www.iaap.org.uk/downloads/codex.pdf).	The suggested parts are added in the sentences. As the posology is concerned, a 2-3 x

	<p>This supplement will contain the manufacturing methods of the <i>Viscum album</i> containing preparations of Iscador and Helixor. The Swiss Pharmacopoeia refers to this Anthroposophic Pharmaceutical Codex for specific anthroposophic production processes (see section "Anthroposophic Preparations" in Swiss Pharmacopoeia; Ph Helv 10 Supplementum 10.2).</p> <p>Furthermore, we are not aware that methods of production of those plants/plant parts that have been granted a WEU indication in an HMPC monograph are available in the public domain. We assume that you may refer to the Hager's Encyclopaedia which contains very outdated information about <i>Visci albi herba recens</i>.</p> <p>The production methods of the Abnobaviscum preparations (anthroposophic authorizations) are for example published in HAB (German Homoeopathic Pharmacopoeia, rule 32).</p> <p>In light of the above comments, please amend the sentence as follows: "The method of production for some of the extracts is not yet in the public domain."</p> <p>- As an example, we checked for Iscador whether the host plant was given in the publications referred to in the DAR and listed in the "List of References".</p> <p>Out of 47 publications that refer to Iscador (books & reviews not considered), in 25 the host plant was given and in 22 it was missing. The host plant was mainly not given in case of meta-analyses and retrospective analyses where several preparations with different host trees have been analysed together or the type of host plant was not reliably retrievable from the clinical documentation. As soon as the preparation is described in the clinical studies as Iscador including the host plant, this criterion does not apply as the qualitative and</p>	<p>weekly subcutaneous injection is indeed used in anthroposophic practice, but the amount injected may vary from patient to patient.</p>
--	--	---

	<p>quantitative composition of those products is given in the Summary of Product Characteristics.</p> <p>Below is an example given as you will find it in the SmPC for Iscador® P in Austria:</p> <p>Iscador® P 20 mg: 1 ampoule of 1 ml (= 1g) contains: Iscador® P 20 mg 40 mg fermented native liquid extract made out of fresh leaves, stems, buds and berries of pine tree mistletoe (<i>Viscum album</i> subsp. austriacum, DER 1:2, extraction solvent water) equivalent to 20 mg fresh mistletoe herb. Other excipient: approx. 3.2-3.6 mg/ml sodium as sodium chloride, according to strength For the full list of excipients, see section 6.1.</p> <p>6.1 List of excipients Water for injections Sodium chloride</p> <p>Apart from this, the qualitative and quantitative composition of the extracts could be given like this for all mistletoe products in the monograph:</p> <p>“With regard to the marketing authorization application of Article 10(a) of Directive 2001/83/EC, as amended <i>Viscum album</i> L., herba (mistletoe)</p> <p>i) Herbal substance Leaves, stems, buds, blossoms, sinkers, and/or berries from <i>Viscum album</i> L. Hosts can be apple tree (M), oak (Qu), pine (P), fir (A), elm (U), maple (Aceris), almond (Amygdali), birch (Betulae), hawthorn (Crataegi), or ash (Fraxini).</p> <p>ii) Herbal preparations</p>	
--	--	--

	<p>expressed juice ethanol extracts wine extracts fermented and unfermented aqueous extracts tinctures dry extracts"</p> <p>This is in line with what is given in the monograph of <i>Echinacea purpurea</i> (L.) Moench, herba recens which has a WEU-indication and also in line with your description in the right column of the table on page 1 of the assessment report of <i>Viscum album</i>.</p> <p>We therefore suggest rephrasing as follows: "The qualitative and quantitative composition of the extracts used in clinical studies is not always known and will depend on the host plant."</p> <p>- We checked for Iscador as an example if the posology was given in the publications listed in the "List of References supporting the assessment of <i>Viscum album</i> L., herba". Out of 47 publications that refer to Iscador (books & reviews not considered), in 30 the posology was given, in 15 it was missing and in 2 it was not given due to the fact that those are analytical/ preclinical papers. Standard posologies can be derived from the Summary of Product Characteristics of all mistletoe products (see also proposed table in section 2.3). The standard posology of all herbal products of anthroposophic mistletoe manufacturers is independent of the host tree. It is: 2-3 x weekly subcutaneous injection. In case of Iscador® one dose is equivalent to 1 ml of product.</p> <p>We hence suggest to correct the sentence as follows:</p>	
--	---	--

		"Standard posologies could not always be derived from the clinical studies."	
4.3. Oncology	IAAP	<p>The HMPC states that the method of production of the extracts is not in the public domain. The IAAP wishes to draw your attention to the document "Anthroposophic Pharmaceutical Codex", APC (second edition), which can be seen and downloaded from the internet at http://www.iaap.org.uk/downloads/codex.pdf</p> <p>The APC, which is in public domain, contains some information concerning the manufacture of <i>Viscum album</i> preparations used in oncology:</p> <p>At pp. 75/76 you can find that information.</p> <p>At the link http://www.iaap.org.uk/quality/downloads/Explanatory_Note-Viscum_album-09-01-2008.pdf which is an "Explanatory note", the connection to <i>Viscum album</i> preparations is given.</p> <p>The IAAP is actually working on a substantial revision of the APC which will contain much more information on the preparation of concerning <i>Viscum album</i> preparations. We foresee the publication ca 06.2012. We plan to communicate the publication to the chairman of the HMPC and to the rapporteur of the <i>Viscum album</i> monograph.</p>	<p>In the adapted version of the assessment report a paragraph is added under section 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof:</p> <p><i>The "Anthroposophic Pharmaceutical Codex", APC (second edition 2007), which can be seen and downloaded from the internet at http://www.iaap.org.uk/downloads/codex.pdf, contains information concerning the manufacturing of <i>Viscum album</i> preparations used in oncology.</i></p> <p>Under section 1.1. of the AR it reads now:</p> <p>- <i>Although the Anthroposophic Pharmaceutical Codex contains information on general principles for preparing extracts, details of production of some specific extracts is not yet in the public domain.</i></p>
5.3 Adverse events and serious adverse events and deaths (page 19)	AESGP	<p>Please complete sentence (reason see above):</p> <p>"No further details are included in this assessment report, as they are related to an oncological use of <i>Viscum</i> and this use falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3)."</p>	The sentence is added.
5.5 Safety in special	AESGP	Drug interactions:	More recent and specific references are

populations and situations (page 19)		The reference is not up to date and substantiated. It should hence be modified as follows: “Caution must be taken in consideration of potential interactions of <i>Viscum album</i> extracts and other components with similar or opposing effects (Barnes et al. 2007) Drug interactions seem rather unlikely from the point of <i>in vitro</i> (Doehmer et al. 2012) and clinical investigations (Mansky et al. 2011) conducted with various mistletoe preparations.”	added as suggested.
5.6 Overall conclusions on clinical safety	AESGP	ONCOLOGY (page 20): It should be justified why no analysis was made. We propose the following statement: “No analysis was made because oncological use of <i>Viscum album</i> falls outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products and the evaluation with respect to well-established use is not yet possible because some essential criteria for evaluation are not fulfilled (see section 4.3). No analysis was made.”	The suggested justification for not making a monograph is included.
6. Overall conclusions	AESGP	ONCOLOGY (page 20-21) For the reasons mentioned above, please modify as follows: - The method of production for some of the extracts is not yet in the public domain. - - The qualitative and quantitative composition of the extracts used in clinical studies is not always known and will depend on the host plant. - Standard posologies could not always be derived from the clinical studies.	The specifications are included in the revised version of the assessment report.
Draft Public Statement	IVAA	IVAA agrees with the first conclusion of the draft Public Statement on the use of <i>Viscum album</i> in cancer therapy, that this lies only outside the scope of chapter 2a (specific provisions Comments on Draft Assessment report on <i>Viscum album</i> L, herba Page 3 3 applicable to traditional herbal medicinal products) of Directive 2001/83/EC. Thus, we understand that the reference to “Directive 2001/83/EC as amended for	The period of 2006 – 2011 was chosen for the most recent literature search. For publications < 2006 review articles and standard books were used: e.g. Keller et al. (1994), Kienle & Kiene (2003), Horneber (2008), Lange-Lindberg (2006).

		<p>traditional herbal medicinal products” means reference to “Directive 2004/24/EC”.</p> <p>We take note of the fact that the assessors restricted themselves to literature published between 2006 and 2010, and did not consider the larger reviews and meta-analyses in the public domain.</p>	<p>An extended assessment report was submitted to the MLWP and the HMPC. This version of the assessment report contained tabled overviews of clinical studies with patients suffering from different types of cancer, inclusion and exclusion criteria, treatment regimens, therapeutic outcomes as well as side effects seen during these clinical trials. For reasons mentioned in the actual assessment report and the public statement the MLWP and the HMPC, after having reflected on the content, finally decided not to publish an extended evaluation and to guarantee a concordance between the public statement and (a limited) assessment report.</p> <p>Nevertheless, more recent references have been inserted as suggested, without further commenting them.</p>
Assessment report in general	IVAA	<p>As research on <i>Viscum album</i> continues at high speed, some data in the report had already been outdated and some may be outdated in near future. This mainly concerns historical data, the regulatory status, information on use and indications, and some toxicological and clinical data. With regard to non-clinical and clinical data available in the public domain, and having in mind ongoing scientific research on <i>Viscum album</i>, as well as the announced publication/revision of the above mentioned monographs, we see a need to review the assessment report and/or to re-consider the establishment of a mistletoe monograph in the</p>	<p>The MLWP and the HMPC are aware of the intensive clinical investigations made with <i>Viscum album</i>. More recent references have been included in the revised version of the assessment report.</p> <p>However, the option for a public statement instead of a monograph for <i>Viscum album</i> has been extensively discussed within the MLWP and the</p>

		near future including more recent data.	HMPC. As no majority could be found for a monograph, in the final public statement supported by the AR the reasons are explained why such a monograph cannot be developed.
Historical data on medicinal use General	Phytolab	<u>Mistletoe herb (<i>Viscum album</i> L.) (Visci alba herba)</u> The medicinal use of Visci alba herba in Europe can be traced back to middle age. For example LONICERUS (1564) and TABERNAEMONTANUS (1731) describe the use against dizziness and tumours. (according to KOOPERATION PHYTOPHARMAKA 2006) Mistletoe is named in the „Straßburger Arzneibuch“ of Strasbourg (1725) and in the „Preußische Arzneitaxe“ of Prussia (1715) (according to BERGER 1950). A monograph for <i>Viscum album</i> was enclosed in the Pharmacopoea of Prussia in 1846 (according to SPAICH 1977). According to GAULTHER (1907) focused the medicinal use of Mistletoe since approx. 1910 on the blood pressure lowering properties (according to MADAUS 1938). In the monograph Viscum of The British Pharmaceutical Codex (1934) is written that the herb has been used for lowering blood pressure, and it is also said to lessen the cardiac impulse and to relieve precordial distress, effects which are probably due to dilation of the peripheral vessels. MADAUS (1938) summarises the main indications as follows: reduction of blood pressure, arteriosclerosis and hypertension. In the monograph Herba Visci albi of the Supplement to DAB 6 (Erg.-B. 6 1953) a single dose of 2.5 g per 1 cup cold water is described. The British Herbal Pharmacopoeia (1983) names the indications high blood pressure, arteriosclerosis, nervous tachycardia and hypertensive headache, the dosage for infusion is 3 times daily 2-6 g dried leaves, also as cold infusion. 1987 a monograph „Mistelkraut“ was published in DAC, since 1993 the monograph „Mistelkraut“ is enclosed in DAB. The	There is a lot of historical information on traditional cardiovascular use indeed. Table 1 of the overview of comments is now inserted in the assessment report

		<p>British Herbal Pharmacopoeia (1996) names hypotensive as action. COMMISSION E (1984) lists the uses: treating of degenerative inflammation of the joints and palliative therapy for malignant tumors through non-specific stimulation. It is noted that the blood pressure-lowering effects and the therapeutic effectiveness for mild forms of hypertonia (borderline hypertonia) need further investigation. A Mistletoe herb tea with the indication „Traditionally used to improve the cardiovascular function“ was added to the list of indications according to Section 109a German Medicines Act (Indikationsliste nach § 109a AMG) in 1995.</p> <p>Currently (April 2011), the Committee on Herbal Medicinal Products (HMPC) is discussing the Draft of the Community Herbal Monograph on <i>Viscum album</i> L., herba.</p>	
<p>Historical data on medicinal use</p> <p>General</p>	Phytolab	<p><i>Traditional usage of mistletoe herb</i></p> <p>The medicinal use of mistletoe herb (<i>Visci alba herba</i>) for circulatory complaints can be traced back in Europe until the 17th century. The following summary of references like pharmacopoeia, standard literature and official documents demonstrates the traditional use of motherwort herb. Especially the application as tea and the medicinal use within the European Community since the beginning of the 20th century is pointed out.</p> <p>See also table in annex.</p>	See the answer to the former comment.
<p>Historical data on medicinal use</p> <p>Mistletoe tea</p>	Phytolab	<p>Mistelkraut Tee is a traditional herbal medicinal product used to improve circulatory function. Active pharmaceutical ingredient is dried mistletoe herb (<i>Viscum album</i> L., herba). Excipients are not contained.</p> <p>100 g Mistelkraut Tee contains: Active pharmaceutical ingredient:</p>	Mistletoe tea is included in the assessment report.

		<p>Mistletoe herb 100 g</p> <p>The dose recommendation for Mistelkraut Tee for adolescents, adults and elderly is 2 times daily a cup of tea prepared with 1 tea bag at 2.0 g. The daily dose is 4g</p> <p>The use in children under 12 years of age is not recommended.</p> <p>The tea is prepared as follows: 150 ml cold water is poured over 1 tea bag Mistelkraut Tee, infuse 12 hours at room temperature, take out the tea bag and boil short-time.</p>	
Plausibility of Dosage	Phytolab	<p>No dose recommendations for <u>orally</u> administered mistletoe preparations are given in the monograph of the German Commission E on mistletoe herb, which describes only the use of solutions for injections (BLUMENTHAL 1998).</p> <p>According to the literature (HAGER 2006) for the treatment of hypertension and prophylaxis of arteriosclerosis the following doses of mistletoe herb are used:</p> <p>herbal drug: 2 to 6 g powdered mistletoe herb 3 times daily herbal tea: 2.5 g fine cut herbal drug (1 tea spoon) as a cold infusion, 1 to 2 times daily mistletoe wine: 40 g herbal drug / 1 l wine, 3 to 4 glasses daily Extractum Visci fluidum EB 6: medium single dose 0.5 g Spiritus Visci compositus EB 6: medium single dose 5.0 g mistletoe liquid extract BHP 83: 1 to 3 ml up to 3 times daily mistletoe tincture BHP 83: 0.5 ml 3 times daily</p> <p>The dosage form of Mistelkraut Tee is a herbal tea consisting of cut mistletoe herb. The dose recommendation for Mistelkraut Tee for adolescents, adults and elderly is two times daily 2 g herbal tea</p>	The recommended doses of herbal monopreparations with <i>Viscum album</i> are taken to the assessment report.

		<p>(correspondingly one filter bag) extracted with 150 ml cold water for twelve hours and boiled up prior to intake. Thus, the maximal daily dose of the active substance corresponds to 4 g mistletoe herb. The use in children under 12 years of age is not recommended.</p> <p>Thus, the dosage of the active substance is comparable with the respective recommendations from the literature (5 g fine cut herbal drug as a cold infusion) and is below the highest available dosage specification for mistletoe herb (maximum daily dose of 18 g powdered drug) (HAGER 2006). Comparable products (e.g. <i>Bad Heilbrunner Misteltee</i> (registration no. 75317.00.00), which are equivalent in mode of administration, dosage and indication to Mistelkraut Tee are registered as Traditional Medicinal Product according to §39b/§39c AMG in Germany. Hence, when used according to the recommendations Mistelkraut Tee is considered to be safe and well tolerated. Due to the longstanding traditional use of the product in the claimed indication the efficacy is also considered to be plausible from the expert's point of view.</p> <p>Overall, the recommended dosage of Mistelkraut Tee is regarded as plausible with respect to both efficacy and safety.</p>	
Conclusion	Phytolab	<p>The finished medicinal product Mistelkraut Tee contains mistletoe herb as single pharmaceutical active ingredient. The indication of the herbal tea Mistelkraut Tee is "traditionally used to improve circulatory function". The dosage is 2 times daily 1 cup of tea at 2.0 g mistletoe herb.</p> <p>The traditional medicinal usage of herbal teas containing mistletoe herb as single pharmaceutical active ingredient within Europe, especially in Germany, can be documented over more than 30 years.</p> <p>Numerous teas as finished medicinal products in the field of indication circulatory function containing as only active pharmaceutical ingredient</p>	This practical information provided by Phytolab is mentioned in the assessment report.

	<p>mistletoe herb are listed. These finished medicinal products are on the German market from at least 1976 until 2007, 2010 and today, respectively. <i>Bad Heilbrunner Misteltee</i> (registration no. 75317.00.00) has got a registration as Traditional Medicinal Product according to §39b/§39c AMG, dated 08.10.2009. Composition, mode of administration, dosage and indication of Mistelkraut Tee is equivalent to <i>Bad Heilbrunner Misteltee</i>.</p> <p>Additionally, the traditional use of mistletoe herb for tea preparation in the field of indication circulatory function is shown. The traditional single and daily dose of Mistelkraut Tee is in the traditional range. The composition, mode of administration, and the field of indication of Mistelkraut Tee are equivalent to No. 257 of "Indikationsliste nach § 109a AMG".</p> <p>So the traditional medicinal usage of the composition, mode of administration, dosage and indication of Mistelkraut Tee can be stated as proved for more than 30 years.</p> <p>Mistletoe herb is widely used herbal drug which has been used for a long time for the treatment of circulatory complaints, especially mild forms of hypertension.</p> <p>The preclinical and toxicological data on mistletoe preparation are scarce. However, the Hager monograph and the accomplished literature research did not reveal any hint on relevant toxic effects. There is no suspicion for a possible genotoxic or carcinogenic effect of mistletoe herb.</p> <p>The preclinical and toxicological data do not give reason for any concern with regard to the safety profile of orally used mistletoe.</p> <p>In summary, the tolerability profile of Mistelkraut Tee is very good.</p>	
--	--	--

		<p>When used according to the recommendations no risks are expected. From the expert's point of the following warning notes should be included in the product information:</p> <p>Known allergy to the active substance (mistletoe) Due to the lack of adequate data the use of Mistelkraut Tee is not recommended in children under 12 years of age. Use mistletoe herb in adolescents younger than 18 years only after consultation with a physician. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.</p> <p>Overall, due to the long-standing use in humans and the generally acknowledged pharmacological effects of mistletoe herb the indication <i>"traditionally used to improve circulatory function."</i></p> <p>is plausible. The benefit/risk ratio of Mistelkraut Tee is clearly positive, and its registration under the dispensing category E is endorsed from a medicinal point of view.</p>	
--	--	--	--

AR = Assessment Report

ANNEXES (annexed information provided by Interested Parties)

Annex 1 Phytolab Table 1.

Annex 2 Phytolab Table 2.

Annex 3 Phytolab list of references

Annex 4 AESGP Table 3.

Annex 5 AESGP list of references

Annex 1 Phytolab Table 1.

Traditional usage of mistletoe herb

The medicinal use of mistletoe herb (*Visci alba herba*) for circulatory complaints can be traced back in Europe until the 17th century.

The following summary of references like pharmacopoeia, standard literature and official documents demonstrates the traditional use of motherwort herb. Especially the application as tea and the medicinal use within the European Community since the beginning of the 20th century is pointed out.

Table 1: Traditional usage of mistletoe herb

Jahr	Quelle	Angaben zur Anwendung
1564	LONICERUS (acc. to Kooperation Phytopharmaka 2006)	„... banishes dizziness and tumours of the body. In case of permanent bleeding of the nose ... stops bloody vomiting.“
1731	TABERNAEMONTANUS (acc. to Kooperation Phytopharmaka 2006)	„... it is also effective against dizziness ... crushed leaves are said to cure crippled limbs. It partitions and softens tumours.“
1715	Preußische Arzneitaxe (acc. to BERGER 1950)	Monograph <i>Viscum album</i>
1725	Straßburger Arzneibuch (acc. to BERGER 1950)	Monograph <i>Viscum album</i>
1846	Preußische Pharmacopoe (acc. to SPAICH 1977)	Monograph <i>Viscum album</i>
1934	The British Pharmaceutical Codex	Monograph <i>Viscum</i> <i>Action and Use:</i> On account of its vasodilator action, mistletoe has been used for lowering blood pressure. Its action is usually delayed and a maximum effect is reached three to four days after the commencement of treatment. It is also said to lessen the cardiac impulse and to relieve precordial distress, effects which are probably due to dilation of the peripheral vessels. It has also been found useful in cases of hysteria and chorea.

Jahr	Quelle	Angaben zur Anwendung
		<u>Dosage:</u> Mistletoe is administered as a soft extract in pills, or as an infusion or tincture (1 in 8).
1938	MADAUS	<u>Indication:</u> Reduction of blood pressure, for arteriosclerosis and hypertension, as well as dizziness. <u>Dosage:</u> 0.6-1.8 g of the stems several times daily; 1-1.5 g of the powder.

Jahr	Quelle	Angaben zur Anwendung
1941	Potter 's Cyclopaedia	Monograph Mistletoe, leaves. <u>Actions:</u> Nervine, antispasmodic, tonic, narcotic. Has been used with benefit in hysteria, epilepsy, and other nervous diseases. Is of value in uterine haemorrhages, in amenorrhoea and dysmenorrhoea, and as a heart tonic in typhoid fever, also for blood pressure. <u>Dosage:</u> 1.9 – 7.8 g powdered leaves
1950	BERGER	Folia Visci. <u>Indications:</u> Hypertonia, cardiac asthma, and arteriosklerosis. Cardiac, diseases of the circulatory system, cardiac insufficiency, dropsy, nervous states. <u>Dosage:</u> Infus with cold water: 1 teaspoonful per 1 cup of cold water, drink in 3 portions during the next day; or as powder (1.0-1.5 g per day).
1953	Erg.-B. 6	Monograph Herba Visci albi. <u>Dosage:</u> 2.5 g dried drug (per 1 cup cold water)
1967	Extra Pharmacopoeia, Martindale, 25. Edition	Monograph Mistletoe <u>Uses:</u> Mistletoe has a vasodilator action and is used for lowering blood-pressure . Its action is usually delayed and a maximum effect is reached three to four days after the commencement of treatment. It is also said to lessen the cardiac impulse and to relieve precordial distress, effects which are probably due to dilation of the peripheral vessels. It has also been found useful in cases of hysteria and chorea. <u>Dosage:</u> Mistletoe is administered as a soft extract in pills, or as an infusion or tincture (1 in 8).
1974,	WEISS	Mistletoe herb is lowering the blood pressure , for mild hypertonia.

Jahr	Quelle	Angaben zur Anwendung
1990		Infus with cold water: 2 - 4 teaspoonful in 250 ml cold water, 12 h at room temperature, 1 cup in the morning and 1 cup in the evening.
1975	HOPPE	Mistletoe extracts for hypertonia and arteriosklerosis
1976, 1983	British Herbal Pharmacopoeia	Monograph Viscum <u>Indications:</u> High blood pressure, arteriosclerosis, nervous tachycardia, hypertensive headache, chorea, hysteria; arterial hypertension. <u>Dosage:</u> 2-6 g dried leaves or by infusion, thrice daily. Infusion 1:20 in cold water.
1977	SPAICH	Arteriosklerosis, hypertension, dizziness, headache, excitability, neuralgia

Jahr	Quelle	Angaben zur Anwendung
1979	HAGER	Monograph Herba Visci. For arthrosis, spondylosis, neuritides, chronic arthropathy; as adjuvant for hypertonia. Prophylaxis and therapy of tumours. In folk medicine for epilepsy, dizziness, amenorrhagia.
1984	WICHTL	Monograph Mistelkraut (Visci alba herba) <u>Indication:</u> Adjuvant in hypertension, dizziness. In folk medicine for dizziness, amenorrhea, arthropathy. <u>Dosage:</u> 2.5 g cut herb per 1 cup cold water, 12 h at room temperature. Drink 1 - 2 cups daily (1 teaspoonful = ca. 2.5 g)
1984	German COMMISSION E	Monograph Mistletoe herb (Visci alba herba) For treating degenerative inflammation of the joints by stimulating cuti-visceral reflexes following local inflammation brought about by intradermal injections. As palliative therapy for malignant tumors through non-specific stimulation. Note: The blood pressure-lowering effects and the therapeutic effectiveness for mild forms of hypertonia (borderline hypertonia) need further investigation.
1987	DAC	Monograph Mistelkraut
1989	Martindale 29th edition	<u>Uses:</u> Mistletoe has a vasodilator action and is used for lowering blood-pressure. Its action is usually delayed with a maximum effect reached 3 to 4 days after the commencement of treatment. It has also been used in hysteria and chorea and was

Jahr	Quelle	Angaben zur Anwendung
		reputed to be of use as antineoplastic agent.
1991	Normdosen	Single dose: 2.5 g Visci albi herba per cup cold water
1993	DAB	Monograph Mistelkraut (Visci alba herba)
1994	Český Farmaceutický Kodex	Monograph Visci albi herba
1995	Indikationsliste nach § 109a AMG BAnz. No. 190 dated 10.10.1995 <i>Annotation:</i> Traditional medicinal products which have completed a post-marketing approval procedure (pursuant to Section 105 AMG in conjunction with Section 109a AMG). BAnz. = Bundesanzeiger (federal gazette; announcement regarding all relevant alterations about a marketing authorisation or registration).	No. 257: Mistletoe herb, tea, traditionally used to improve the cardiovascular function. From 1995 to 2000, 4 further positions of the list of indications acc. to § 109a AMG have been published, which contain mistletoe herb in a tea formulation used to improve the cardiovascular function (No. 59, 9831001, 1002).
1996	British Herbal Pharmacopoeia	<i>Action:</i> Hypotensive

Jahr	Quelle	Angaben zur Anwendung
1999	DAB 1999	Monograph Mistelkraut (Visci alba herba)
1999	Martindale 32nd edition	<i>Uses:</i> Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders.
2001	VALNET	Monograph „Gui“ (<i>Viscum album</i>) <i>Indications:</i> Arteriosclerosis, hypertension and its troubles, migraine, asthma, menopause and its symptoms like palpitations, tachycardia, circulatory troubles, dyspnoe <i>Dosage:</i> 1-2 pinches cut leaves or young stems per cup boiling water, infuse for 10 minutes. 2 cups daily between meals.
2003	Potter´s Cyclopaedia	Mistletoe, young leafy twigs.

Jahr	Quelle	Angaben zur Anwendung
		<u>Use:</u> Hypotensive, cardiac tonic, immunostimulant, antineoplastic, sedative, antispasmodic (according to Potter 1956). Mistletoe was formerly used for high blood pressure and tachycardia, and as a nervine; however the anti-cancer effects are now the most important.
2010	HAGER-ROM	Monograph Visci alba herba <u>Use:</u> In folk medicine for hypertension, also epilepsy, pertussis, asthma, dizziness, amenorrhoea, diarrhoea, chorea, nervous tachycardia, hysteria and nervousness. <u>Dosage:</u> Tea for hypertension and prophylaxis of arteriosklerosis: 2.5 g cut drug per cup of cold water, 12 h at room temperature, 1 - 2 cups daily. Powdered mistletoe herb: 2 6 g, 3 times daily.

Traditional usage of Mistelkraut Tee

The finished medicinal product **Mistelkraut Tee** contains mistletoe herb as single pharmaceutical active ingredient. The indication of the herbal tea **Mistelkraut Tee** is "traditionally used to improve circulatory function". The dosage is 2 times daily 1 cup of tea at 2.0 g mistletoe herb.

The traditional medicinal usage of herbal teas containing mistletoe herb as single pharmaceutical active ingredient within Europe, especially in Germany, can be documented over more than 30 years.

Table 2 shows a selection of numerous other teas as finished medicinal products in the field of indication circulatory function containing as only active pharmaceutical ingredient mistletoe herb. These finished medicinal products are on the German market from at least 1976 until 2007, 2010 and today, respectively. Bad Heilbrunner Misteltee (registration no. 75317.00.00) has got a registration as Traditional Medicinal Product according to §39b/§39c AMG, dated 08.10.2009. Composition, mode of administration, dosage and indication of **Mistelkraut Tee** is equivalent to Bad Heilbrunner Misteltee.

Additionally, the traditional use of mistletoe herb for tea preparation in the field of indication circulatory function is shown in **table 1**. The traditional single dose of mistletoe herb (leaves, stems) per cup is between 0.6-1.8 g (MADAUS 1938), 2.5 g (BERGER 1950, Erg.-Bd. 6 1953, WICHTL 1984, Normdosen 1991, HAGER 2010) and 2-6 g per cup (British Herbal Pharmacopoeia 1976 and 1983), another dose recommendation is 5-10 g per 250 ml for 2 cups (WEISS 1974). The traditional daily dose is between 1-2 times (WICHTL 1984, HAGER 2010), 2 times (WEISS 1974, VALNET 2001), 3 times (Berger 1950, British Herbal Pharmacopoeia 1976 and 1983) and several times (MADAUS 1938) daily 1 cup. So the dosage of **Mistelkraut Tee** is in the traditional range.

Furthermore, the composition, mode of administration, and the field of indication of **Mistelkraut Tee** are equivalent to No. 257 of "Indikationsliste nach § 109a AMG" (see **table 1**).

So the traditional medicinal usage of the composition, mode of administration, dosage and indication of **Mistelkraut Tee** can be stated as proved for more than 30 years.

Enclosed you will find:

A time table for the traditional usage of **Mistelkraut Tee** (*table 2*, p. 7-8)

References to table 2 which are written in cursive letters are enclosed (p. 9-47). The other references can be found under module 2.5.5 *References*.

Annex 2 Phytolab Table 2.

Table 2: Traditional usage of Mistelkraut Tee

Period	Designation	Mode of administration	Active ingredient	Single Dose	Daily Dose	Indication	References
Application for registration as traditional herbal medicinal product							
since 2010	Bad Heilbrunner Mistelkrauttee	tea (tea bags à 2.0 g)	Visci alba herba	2.0 g	4.0 g	Traditionally used to improve circulatory function	AMIS
Registration of a Traditional Medicinal Product according to § 39b/ § 39c AMG dated 08.10.2009, No 75317.00.00, Marketing authorisation holder: Bad Heilbrunner Naturheilmittel GmbH & Co.							
1976 - 2010	Bad Heilbrunner Mistelkrauttee	tea (tea bags à 2.0 g)	Visci alba herba	2.0 g	4.0 g	Traditionally used to improve circulatory function	AMIS
Post-marketing authorisation according to Art. 3 section 7/ 105 AMG, No 6577515.00.00, Cancellation 10/2009, Marketing authorisation holder: Bad Heilbrunner Naturheilmittel GmbH & Co.							
1976 - today	H & S Kreislauftee Mistel	tea (tea bags à 2.0 g)	Visci alba herba	2.0 g per cup cold water, infuse for 1-2 hours and boil afterwards	2-3 cups (4.0 – 6.0 g)	Traditionally used to improve circulatory function	AMIS, PIL 11/2004
Post-marketing authorisation according to Art. 3 section 7/ 105 AMG No 6327497.00.00, Marketing authorisation holder: H & S Teegesellschaft mbH & Co. KG							

Period	Designation	Mode of administration	Active ingredient	Single Dose	Daily Dose	Indication	References
1976 - today	Kneipp Mistel-Tee	tea (tea bags à 2.0 g)	Visci alba herba	2.0 g per cup boiling water, infuse for 5-10 minutes	2-3 cups after meals (4.0 – 6.0 g)	Traditionally used to improve circulatory function	<i>AMIS</i> , <i>PIL 3/2003, 5/2008</i> Selbstmedikationsliste 1994
Post-marketing authorisation according to Art. 3 section 7/ 105 AMG No 6303895.00.00, Marketing authorisation holder: Kneipp-Werke Kneipp-Mittel-Zentrale GmbH & Co. KG							
1976 - 2007	Sidroga Misteltee	tea (tea bags à 2.0 g)	Visci alba herba	2.0 g per cup boiling water, infuse for 5-10 minutes. Or infuse for 10 hours with cold water and boil afterwards.	3 cups (6.0 g)	Traditionally used to improve circulatory function (AMIS) Traditionally used as mild medicinal product for high blood pressure and nervous cardiac complaints (1996)	<i>AMIS</i> Präparate-Liste 1994
Post-marketing authorisation according to Art. 3 section 7/ 105 AMG No 6383113.00.00, Cancellation 10/2006, Marketing authorisation holder: Sidroga GmbH							

References which are written in *cursive* letters are enclosed afterwards. The other references can be found under module 2.5.5 *References*

Herbal medicinal product information

Aufgußbeutel
Text der Packungsbeilage
= Text der äußeren Umhüllung (Faltschachtel)

Gebrauchsinformation

KNEIPP® Mistel-Tee

Wirkstoff: Mistelkraut

Zusammensetzung:

1 Aufgußbeutel KNEIPP Mistel-Tee enthält:

Arzneilich wirksamer Bestandteil:
Mistelkraut, geschnitten 2,0 g

Sonstige Bestandteile:
Keine.

Darreichungsform und Art der Anwendung:

Arzneitee zur Bereitung eines Teeaufgusses

Inhalt: 10 Aufgußbeutel mit Faden à 2,0 g

Indikationsgruppe:

Traditionelles pflanzliches Arzneimittel.

Name und Anschrift des pharmazeutischen Unternehmers und des Herstellers:

KNEIPP-WERKE
D-97064 Würzburg

Anwendungsgebiete:

Traditionell angewendet zur Unterstützung der Kreislauf-Funktion. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung.

Hinweis:

Beim Auftreten von Krankheitszeichen, insbesondere bei zu hohem Blutdruck, sollte ein Arzt aufgesucht werden.

Gegenanzeigen:

Wann dürfen Sie KNEIPP Mistel-Tee nicht einnehmen?

Sie dürfen KNEIPP Mistel-Tee nicht einnehmen, wenn Ihnen bekannt ist, daß Sie auf Mistelkraut überempfindlich reagiert haben.

Zur Anwendung von KNEIPP Mistel-Tee bei Kindern liegen keine ausreichenden Untersuchungen vor. KNEIPP Mistel-Tee soll deshalb bei Kindern unter 12 Jahren nicht angewendet werden.

Was müssen Sie in Schwangerschaft und Stillzeit beachten?

KNEIPP Mistel-Tee darf wegen nicht ausreichender Untersuchungen in der Schwangerschaft und Stillzeit nicht angewendet werden.

Vorsichtsmaßnahmen für die Verwendung:

Keine bekannt.

Wechselwirkungen mit anderen Mitteln:

Keine bekannt.

Warnhinweise:

Keine.

Dosierungsanleitung und Art der Anwendung:

Den Teebeutel mit kochendem Wasser aufgießen und 5–10 Minuten in der abgedeckten Tasse ziehen lassen. Je nach Geschmack kann der Tee mit Honig, Zucker oder Süßstoff gesüßt werden.

Soweit nicht anders verordnet, 2-3 mal täglich 1 Tasse nach den Mahlzeiten trinken.

Nebenwirkungen:

Keine bekannt.

Hinweis: Sollten Sie unerwünschte Wirkungen feststellen, informieren Sie bitte Ihren Arzt oder Apotheker.

Verfalldatum und Aufbewahrung:

Nicht über 25°C aufbewahren.

Das Arzneimittel soll nach Ablauf des Verfalldatums nicht mehr angewendet werden.

Vor Licht und Feuchtigkeit geschützt aufbewahren.

Arzneimittel für Kinder unzugänglich aufbewahren.

Stand der Information:

März 2003

Ch.-B.: ...

Verwendbar bis ... (Monat/Jahr)

Zul.-Nr.: 6303895.00.00

**Text der Packungsbeilage gemäß § 11 AMG
+ Beschriftung der äußeren Umhüllung gemäß § 10 AMG
(= Faltschachtel)**

Arzneitee

kreislaufunterstützend

Zur Einnahme nach Bereitung eines Teeaufgusses.

Gebrauchsinformation

Kneipp® Mistel Tee

Mistelkraut

Stoff- oder Indikationsgruppe:

Traditionelles pflanzliches Arzneimittel.

Anwendungsgebiete:

Traditionell angewendet zur Unterstützung der Kreislauf-Funktion.

Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung.

Hinweis:

Beim Auftreten von Krankheitszeichen, insbesondere bei zu hohem Blutdruck, sollte ein Arzt aufgesucht werden.

Gegenanzeigen:

Wann dürfen Sie Kneipp® Mistel Tee nicht einnehmen?

Sie dürfen Kneipp® Mistel Tee nicht einnehmen, wenn Ihnen bekannt ist, dass Sie auf Mistelkraut überempfindlich reagiert haben.

Zur Anwendung von Kneipp® Mistel Tee bei Kindern liegen keine ausreichenden Untersuchungen vor. Kneipp® Mistel Tee soll deshalb bei Kindern unter 12 Jahren nicht angewendet werden.

Was müssen Sie in Schwangerschaft und Stillzeit beachten?

Kneipp® Mistel Tee darf wegen nicht ausreichender Untersuchungen in der Schwangerschaft und Stillzeit nicht angewendet werden.

Vorsichtsmaßnahmen für die Anwendung und Warnhinweise:

Keine bekannt.

Wechselwirkungen mit anderen Mitteln:

Keine bekannt.

Seite 1 von 2

Dosierungsanleitung und Art der Anwendung:

Den Aufgussbeutel mit kochendem Wasser aufgießen und 5 bis 10 Minuten in der abgedeckten Tasse ziehen lassen. Je nach Geschmack kann der Tee mit Honig, Zucker oder Süßstoff gesüßt werden. Soweit nicht anders verordnet, 2- bis 3-mal täglich 1 Tasse nach den Mahlzeiten trinken.

Nebenwirkungen:

Keine bekannt.

Hinweis: Sollten Sie unerwünschte Wirkungen feststellen, informieren Sie bitte Ihren Arzt oder Apotheker.

Verfalldatum und Aufbewahrung:

Nicht über 25° C aufbewahren.
Das Arzneimittel soll nach Ablauf des Verfalldatums nicht mehr angewendet werden.
In der Originalverpackung aufbewahren, um den Inhalt vor Licht und Feuchtigkeit zu schützen.
Arzneimittel für Kinder unzugänglich aufbewahren.

Zusammensetzung:

1 Aufgussbeutel à 2,0 g Kneipp® Mistel Tee enthält:

Wirkstoff:
Mistelkraut, geschnitten 2,0 g

Sonstige Bestandteile:
Keine.

Darreichungsform:

Arzneitee

Inhalt:

10 Aufgussbeutel à 2,0 g

Name und Anschrift des pharmazeutischen Unternehmers und des Herstellers:

Kneipp-Werke
Kneipp-Mittel-Zentrale GmbH & Co. KG
D-97064 Würzburg

Stand der Information:

Mai 2008

Ch.-B.: ...
Verwendbar bis ... (Monat/Jahr)

Zul.-Nr.: 6303895.00.00

Seite 2 von 2

Plausibility of Dosage

No dose recommendations for orally administered mistletoe preparations are given in the monograph of the German Commission E on mistletoe herb, which describes only the use of solutions for injections (BLUMENTHAL 1998).

According to the literature (HAGER 2006) for the treatment of hypertension and prophylaxis of arteriosclerosis the following doses of mistletoe herb are used:

- herbal drug: 2 to 6 g powdered mistletoe herb 3 times daily
- herbal tea: 2.5 g fine cut herbal drug (1 tea spoon) as a cold infusion, 1 to 2 times daily
- mistletoe wine: 40 g herbal drug / 1 l wine, 3 to 4 glasses daily
- Extractum Visci fluidum EB 6: medium single dose 0.5 g
- Spiritus Visci compositus EB 6: medium single dose 5.0 g
- mistletoe liquid extract BHP 83: 1 to 3 ml up to 3 times daily

- mistletoe tincture BHP 83: 0.5 ml 3 times daily

The dosage form of **Mistelkraut Tee** is a herbal tea consisting of cut mistletoe herb. The dose recommendation for **Mistelkraut Tee** for adolescents, adults and elderly is two times daily 2 g herbal tea (correspondingly one filter bag) extracted with 150 ml cold water for twelve hours and boiled up prior to intake. Thus, the maximal daily dose of the active substance corresponds to 4 g mistletoe herb. The use in children under 12 years of age is not recommended.

Thus, the dosage of the active substance is comparable with the respective recommendations from the literature (5 g fine cut herbal drug as a cold infusion) and is below the highest available dosage specification for mistletoe herb (maximum daily dose of 18 g powdered drug) (HAGER 2006). Comparable products (e.g. *Bad Heilbrunner Misteltee* (registration no. 75317.00.00), which are equivalent in mode of administration, dosage and indication to **Mistelkraut Tee** are registered as Traditional Medicinal Product according to §39b/§39c AMG in Germany. Hence, when used according to the recommendations **Mistelkraut Tee** is considered to be safe and well tolerated. Due to the longstanding traditional use of the product in the claimed indication the efficacy is also considered to be plausible from the expert's point of view.

Overall, the recommended dosage of **Mistelkraut Tee** is regarded as plausible with respect to both efficacy and safety.

Conclusion

The finished medicinal product **Mistelkraut Tee** contains mistletoe herb as single pharmaceutical active ingredient. The indication of the herbal tea **Mistelkraut Tee** is "traditionally used to improve circulatory function". The dosage is 2 times daily 1 cup of tea at 2.0 g mistletoe herb.

The traditional medicinal usage of herbal teas containing mistletoe herb as single pharmaceutical active ingredient within Europe, especially in Germany, can be documented over more than 30 years.

Numerous teas as finished medicinal products in the field of indication circulatory function containing as only active pharmaceutical ingredient mistletoe herb are listed. These finished medicinal products are on the German market from at least 1976 until 2007, 2010 and today, respectively. *Bad Heilbrunner Misteltee* (registration no. 75317.00.00) has got a registration as Traditional Medicinal Product according to §39b/§39c AMG, dated 08.10.2009. Composition, mode of administration, dosage and indication of **Mistelkraut Tee** is equivalent to *Bad Heilbrunner Misteltee*.

Additionally, the traditional use of mistletoe herb for tea preparation in the field of indication circulatory function is shown. The traditional single and daily dose of **Mistelkraut Tee** is in the traditional range. The composition, mode of administration, and the field of indication of **Mistelkraut Tee** are equivalent to No. 257 of "Indikationsliste nach § 109a AMG".

So the traditional medicinal usage of the composition, mode of administration, dosage and indication of **Mistelkraut Tee** can be stated as proved for more than 30 years.

Mistletoe herb is widely used herbal drug which has been used for a long time for the treatment of circulatory complaints, especially mild forms of hypertension.

The preclinical and toxicological data on mistletoe preparation are scarce. However, the Hager monograph and the accomplished literature research did not reveal any hint on relevant toxic effects. There is no suspicion for a possible genotoxic or carcinogenic effect of mistletoe herb.

The preclinical and toxicological data do not give reason for any concern with regard to the safety profile of orally used mistletoe.

In summary, the tolerability profile of **Mistelkraut Tee** is very good. When used according to the recommendations no risks are expected.

From the expert's point of the following warning notes should be included in the product information:

- Known allergy to the active substance (mistletoe)
- Due to the lack of adequate data the use of **Mistelkraut Tee** is not recommended in children under 12 years of age.
- Use mistletoe herb in adolescents younger than 18 years only after consultation with a physician.
- Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Overall, due to the long-standing use in humans and the generally acknowledged pharmacological effects of mistletoe herb the indication

“traditionally used to improve circulatory function.”

is plausible. The benefit/risk ratio of **Mistelkraut Tee** is clearly positive, and its registration under the dispensing category E is endorsed from a medicinal point of view.

Annex 3 Phytolab list of references

References

➤ Product-specific documents for other medicinal products

AMIS extracts and PIL are included in this overview of comments.

Other references are available on request.

AMIS	Arzneimittelinformationssystem – Öffentlicher Teil Datenbank-Anbieter: Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) (German database for finished medicinal products) Bad Heilbrunner Mistelkrauttee (75317.00.00) Bad Heilbrunner Mistelkrauttee H&S Kreislauftee Mistel Kneipp Mistel-Tee Sidroga Misteltee
INDIKATIONSLISTE nach §109a AMG	List of indications of traditionally used formulations according to section 109a German Medicinal Act, no. 257 (Bundesanzeiger No. 190 dated 10.10.1995)
PIL 11/2004 H&S Kreislauftee Mistel	Product Information Leaflet 11/2004
PIL 03/2003 Kneipp Mistel-Tee	Product Information Leaflet 03/2003
PIL 05/2008 Kneipp Mistel-Tee	Product Information Leaflet 05/2008
PRÄPARATE-LISTE DER NATURHEILKUNDE	U. Illig, Präparate-Liste der Naturheilkunde, Urban & Schwarzenberg, München 1996 Sidroga Misteltee
SELBSTMEDIKATIONS-LISTE 1994	Selbstmedikationsliste, Bundesfachverband der Arzneimittelhersteller e.V., Deutscher Apotheker Verlag, Stuttgart 1994 Kneipp Mistel-Tee

References

- BASARAN AA, YU T, PLEWA M, ANDERSON D. An investigation of some Turkish herbal medicines in Salmonella typhimurium and in the COMET assay in human lymphocytes, Teratogenesis, carcinogenesis, and mutagenesis, 16, 2, 1996, 125 - 138
- BERGER, F.; Handbuch der Drogenkunde, Bd. 2; Wilhelm Maudrich Verlag, Bonn 1950, p. 372 – 405
- BFARM. 2005.
http://www.bfarm.de/cIn_028/nn_1199044/SharedDocs/Publikationen/DE/Arzneimittel/2_zulassung/zulArten/bes-therap/am-trad/indikatlisterpara109-040824.templateld=raw.property=publicationFile.pdf/indikatlisterpara109-040824.pdf
- BLUMENTHAL M. The complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines, Mistletoe herb, American Botanical Council, 1998
- BRITISH HERBAL PHARMACOPOEIA 1976; Monograph Viscum; British Herbal Medicine Association, London 1976
- BRITISH HERBAL PHARMACOPOEIA 1983; Monograph Viscum; British Herbal Medicine Association, Bournemouth 1983
- BRITISH HERBAL PHARMACOPOEIA 1996; Monograph Mistletoe herb; British Herbal Medicine Association, Bournemouth 1996
- THE BRITISH PHARMACEUTICAL CODEX 1934; Monograph Viscum (Mistletoe); Council of the Pharmaceutical Society of Great Britain; The Pharmaceutical Press, London 1934
- Český Farmaceutický Kodex 1 (Codex Pharmaceuticus Bohemicus Editio prima), Nakladatelství X-EGEM, Praha 1993
- DAB 1993; Monograph Mistelkraut; DAB 10, 2nd supplement 1993
- DAB 1999; Monograph Mistelkraut; DAB 1999
- DAC 1986; Deutscher Arzneimittel-Codex 1986, 4th supplement 1987; Monograph Mistelkraut; Deutscher Apotheker Verlag, Stuttgart 1987
- EFSA, Scientific Opinion, Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health, EFSA Journal, 2011; 9(12):2474
- EMA; Committee for veterinary medicinal products: *Viscum album*. Summary report. EMA/MRL/680/99-Final, August 1999
- EMA. <http://www.emea.europa.eu/htms/human/grd/grdtemplate.htm>, 2009
- EMA/CHMP/203927/2005. Guideline on Risk Assessment of Medicinal Products on Human Reproduction and lactation: from data to Labelling, July 2008
- ERG.-B. 6: Monograph Herba Visci albi (Mistelkraut); supplement to DAB 6; Deutscher Apotheker Verlag, Stuttgart 1953
- EXTRA PHARMACOPOEIA MARTINDALE; 25th Edition; Monograph Mistletoe; Council of the Pharmaceutical Society of Great Britain; The Pharmaceutical Press, London 1967
- HAGER 1979; Monograph Viscum; Hagers Handbuch der Pharmazeutischen Praxis, 6. Band; Springer-Verlag, Berlin 1979

HAGER; Hagers Handbuch der Drogen und Arzneistoffe (CD-Rom). Heidelberg: Springer Verlag, 2006

HAGER-ROM 2010; Monograph Visci albi herba (Mistelkraut); Springer Verlag, Heidelberg 2010

HOPPE, H.A.; Drogenkunde, Bd. 1; Walter de Gruyter, Berlin 1975, S.1135 - 1137

INDIKATIONSLISTE; § 109a AMG, dated 24.08.2004 (List of indications of traditionally used formulations according to section 109a German Medicinal Act)

KAUFHOLD P; PhytoMagister, Modernes und traditionelles Wissen der Pflanzenheilkunde, Richard Pflaum Verlag, München, 2002

KOOPERATION PHYTOPHARMAKA 2006; Medicinal Plants in Traditional Medicine; Krahe Druck GmbH, Unkel 2006

MADAUS, G.; Lehrbuch der biologischen Heilmittel, Bd. III; reprint of issue Leipzig 1938, Georg Olms Verlag, Hildesheim

MARTINDALE; THE EXTRA PHARMACOPOEIA; 29. Edition; Monograph Mistletoe; Council of the Pharmaceutical Society of Great Britain; The Pharmaceutical Press, London 1989

MARTINDALE; THE COMPLETE DRUG REFERENCE; 32. Edition; Monograph Mistletoe; Council of the Pharmaceutical Society of Great Britain; The Pharmaceutical Press, London 1999

NORMDOSEN 1991; Haffner/Schultz/Schmid/Braun, Normdosen der gebräuchlichen Arzneimittel, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1991

OECD. Guidelines for Genetic Toxicology (1983, 1984, 1986), Published by OECD, Paris; latest revisions discussed at ad hoc expert committee meeting, Rome, September 1994, 1994

PORA A, POP H, ROSCA D, RACHU A. Der Einfluß der Wirtspflanze auf den Gehalt an hypotensiven und herzwirksamen Prinzipien der Mistel (*Viscum album* L.), Pharmazie, 12, 8, 1957, 528-538

POTTER'S CYCLOPAEDIA 1941; Potter's Cyclopaedia of Botanical Drugs and Preparations; Potter & Clarke Ltd., London 1941, p. 236 - 237

POTTER'S HERBAL CYCLOPAEDIA 2003; Potter's (Herbal Supplies) Ltd, The C.W. Daniel Company Ltd., Saffron Walden 2003, p. 298 - 299

SPAICH, W.; Moderne Phytotherapie, Karl F. Haug Verlag, Heidelberg 1977, p. 389-393

VALNET, J.; Phytothérapie, Librairie Générale française, Paris 2001, p. 299-300

WEISS, R.F.; Lehrbuch der Phytotherapie, 3. Auflage; Hippokrates Verlag, Stuttgart 1974, p. 167 - 168

WEISS, R.F.; Lehrbuch der Phytotherapie, 7. Auflage; Hippokrates Verlag, Stuttgart 1990, p. 214 - 217

WICHTL, M. 1984; Monograph Mistelkraut; Teedrogen, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1984

WICHTL M; Herbal Drugs and Phytopharmaceuticals. 3 ed. Stuttgart: medpharm GmbH Scientific Publishers, 2004

WIEBELITZ KR, BEER AM. Weißdorn- und Mistelsaft in der Hypertoniebehandlung : hat Mistelsaft additive Effekte?, Komplementäre und integrative Medizin, 48, 1, 2007, 36-41

Annex 4 AESGP Table 3.

Table 3: Systematic Reviews and Meta-Analyses of Clinical Trials with Mistletoe Therapy in Cancer Patients Published between 2006 and 2010

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
<p>Kienle & Kiene Influence of <i>Viscum album</i> L (European mistletoe) extracts on quality of life in cancer patients: A systematic review of controlled clinical studies. Integr Cancer Ther 2010; 1-16. (OnlineFirst, published on May 18, 2010 as doi: 10.1177/1534735410369673)</p> <p>Systematic review</p>	<p>Influence of mistletoe extracts on QoL in cancer patients</p>	<p>AMED, BIOSIS Previews, CAMbase, Cochrane Library, Embase, MEDLINE, NLM gateway, private databases</p>	<p>prospective controlled clinical study or pharmacoepidemiological cohort study, study population with cancer, treatment with mistletoe preparation, QoL outcome; completion of study; published or unpublished ⇒ 26 randomised studies (3,058) and 10 non-randomised studies (4,996; thereof 4,012 in cohort studies) analysed</p>	<p>Half of the studies investigated mistletoe extracts concomitant with chemotherapy, radiotherapy, or surgery. Among the 26 RCTs, 22 reported a QoL benefit, 3 indicated no difference, and 1 did not report any result. All non-RCTs reported a QoL benefit. Improvements were mainly in regard to coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general (less consistently, in regard to pain, diarrhoea, general performance, and side effects of CAOT). Mistletoe therapy was well tolerated.</p>
<p>Kienle et al. <i>Viscum album</i> L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. J Exp Clin Cancer Res 2009; 28: 79-112</p>	<p>Efficacy of mistletoe therapy in breast or gynaecological cancer</p>	<p>AMED, Biosis Previews, Cochrane Library, EMBASE, MEDLINE, NLM gateway, private databases</p>	<p>prospective controlled clinical trial, prospective single-arm cohort study or pharmaco-epidemiological cohort study; study population with breast or</p>	<p>Survival was assessed in 9 randomised controlled trials and in 14 non-randomised controlled trials; 12 reported a statistically significant benefit, the others either a trend or no difference. Tumour behaviour (remission or time to relapse) was assessed in 3 randomised controlled trials and 6 non-randomised</p>

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
Systematic review			gynaecological cancer; treatment with mistletoe preparation; clinically relevant outcome; completion of study; published or unpublished ⇒ 19 randomised (2,420), 16 non-randomised (6,399) controlled clinical studies, and 11 single-arm cohort studies (1,130) analysed	controlled trials; 3 reported a statistically significant benefit, the others a trend, no difference or mixed results. The QoL and tolerability of CAOT or surgery was assessed in 15 randomised controlled trials and in 9 non-randomised controlled trials; 21 reported a statistically significant positive result, the others a trend, no difference, or mixed results. Single-arm cohort studies investigated tumour behaviour, QoL, pharmacokinetics and safety of mistletoe. Tumour remission was observed after high dosage and local application. Mistletoe treatment was well tolerated in the reviewed studies.
Melzer et al. Efficacy and safety of mistletoe preparations (<i>Viscum album</i>) for patients with cancer diseases. Forschende Komplementmedizin 2009; 16(4): 217-26 Systematic review	Efficacy and safety of mistletoe therapy in cancer patients	AMED, BIOETHICSLINE, BIOSIS, CATLINE, CISCOS, Cochrane Complementary Medicine, EMBASE, INT. HEALTH TECHNOLOGY, MEDLINE	controlled trial (randomised or observational), systemic intervention (SC and/or per infusion), evaluation of at least a process-standardised mistletoe preparation, patients with cancer ⇒ 18 studies (>6,800) analysed	Due to heterogeneity between trials a meta-analysis was impossible. Studies indicate improvement of QoL, a reasonable safety profile but inconsistent data on survival or anti-tumour effects.
Melzer & Saller Lebensqualität onkologischer	Influence of supportive	Cochrane Complementary	clinical study on supportive treatment with	Due to heterogeneity of the measures of assessment, i.e. use of diverse uni- or multi-

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
<p>Patienten unter supportiver Behandlung mit <i>Viscum album</i> (parenterale Mistelpräparate). Schweiz Z GanzheitsMedizin 2009; 21(3): 157-61 Systematic review</p>	<p>mistletoe therapy on QoL in cancer patients in the frame of standard cancer therapy</p>	<p>Medicine, EMBASE, MEDLINE.</p>	<p>a parenteral mistletoe preparation, adult patients with solid tumours, evaluable assessment of QoL as a first or secondary endpoint ⇒ 6 studies (nr) analysed</p>	<p>dimensional questionnaires, a calculative meta-analysis could not be performed. There is evidence that supportive treatment with mistletoe preparations is safe and improves QoL independent of the nature of tumour and the preparation used.</p>
<p>Ostermann et al. Survival of cancer patients treated with mistletoe extract (Iscador): a systematic literature review. BMC Cancer 2009; 9: 451 Systematic review</p>	<p>Efficacy of Iscador® in cancer patients with respect to survival</p>	<p>PubMed/MEDLINE, EMBASE, Cochrane Library, DIMDI databases, CAMbase</p>	<p>controlled clinical study on parameters associated with survival in cancer patients treated with Iscador®, published in English or German language journals ⇒ 41 studies (3,388) analysed</p>	<p>The majority of studies demonstrated positive effects in favour of the Iscador® therapy. Heterogeneity of study results was moderate ($I^2=38.3\%$, $p<0.0001$). A random effect meta-analysis estimated the overall hazard ratio at $HR=0.59$ (CI: 0.53–0.66, $p<0.0001$), which indicates that adjuvant cancer treatment with Iscador® is associated with a prolonged survival.</p>
<p>Büssing et al. Quality of life in cancer patients treated with mistletoe extract (Iscador): a meta-analysis. Evidence-Based Complementary and Alternative Medicine 2012; Volume 2012, Article ID 219402, 8 pages Systematic review</p>	<p>Efficacy of Iscador® in cancer patients with respect to QoL associated measures</p>	<p>Cochrane databases, EMBASE, NCCAM, NLM, DIMDI databases, CAMbase, MEDLINE</p>	<p>controlled clinical study, evaluation of parameters associated with QoL, cancer patients, treatment with Iscador®, published in English or German language journals ⇒ 16 studies analysed</p>	<p>Outcome data were extracted and converted into standardised mean differences and their standard errors using standard formulas (Cochrane Handbook). All studies demonstrated positive effects on QoL associated variables in favour of the Iscador® therapy (however, the funnel plot indicates a selection bias). The standardised mean difference ranged from 0.27 to 1.71 with a mean of 0.67, indicating</p>

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
			(1,475)	superiority of Iscador® over control therapies.
Horneber et al. Mistletoe therapy in oncology [reprint]. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD003297. DOI: 10.1002/14651858.CD003297.pub2 Systematic review	Effectiveness, tolerability and safety of mistletoe extracts given either as monotherapy or adjunct therapy for patients with cancer	Cochrane databases, EMBASE, MEDLINE, AMED, BIOETHICSLINE, BIOSIS, CancerLit, CATLINE, CISCOP, HEALTHSTAR, INT. HEALTH TECHNOLOGY ASSESSMENT, SOMED	randomised clinical trial of adults with cancer of any type; treatment with mistletoe extracts as sole treatment or given concomitantly with chemo- or radiotherapy ⇒ 21 studies analysed (3,484)	Of 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The results of 2 trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival. Of 16 trials investigating the efficacy of mistletoe extracts for either improving QoL, psychological measures, performance index, symptom scales or the reduction of AEs of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality. Safety data indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects.
Ziegler & Grossarth-Maticek Individual patient data meta-analysis of survival and psychosomatic self- regulation from published prospective controlled cohort studies for long-term therapy of breast cancer patients with a mistletoe	Efficacy in prospective matched-pair studies including patients with breast cancer	Published prospective matched-pairs studies	published prospective matched-pairs study with breast cancer patients concerning long-term therapy with Iscador® ⇒ 2 randomised (55 matched pairs), 4 non-	Consistency of positive results across randomised and non-randomised studies as well as across different types of statistical analyses could be shown.

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
preparation (Iscador). eCAM 2008; p 1-10 Individual patient data meta-analysis			randomised studies (309 matched pairs) analysed	
Kienle & Kiene Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. Eur J Med Res 2007; 12: 103-19 Systematic review	Efficacy of anthroposophic mistletoe therapy in prospective clinical trials	AMED, Biosis Previews, Cinahl, Cochrane databases, EMBASE, MEDLINE, NLM Gateway, Science Citation Index, National Centre for Complementary and Alternative Medicine, reference lists and extensive expert consultations	prospective controlled clinical trial or prospective single-arm cohort study; study population with cancer; treatment with anthroposophic mistletoe preparation; clinically relevant outcome; completion of study; published or unpublished ⇒ 16 randomised controlled studies (2,602), 9 non-randomised studies (2,512), and 12 prospective cohort studies (251) analysed	Sign. benefit in terms of survival in 8 of 17 trials (5 of 10 randomised trials), in terms of remission of tumour and malignant effusion in 1 randomised and 1 non-randomised out of 4 controlled trials, in terms of QoL in 3 of 5 randomised trials, and in terms of reduction of AEs of CAOT and related improvement of QoL in 5 of 7 trials (3 of 5 randomised trials). No significant benefit for disease-free survival and tumour recurrence (2 randomised controlled trials). None of the studies found a disadvantage of mistletoe therapy.
Lange-Lindberg et al. Misteltherapie als begleitende Behandlung zur Reduktion der Toxizität der Chemotherapie maligner Erkrankungen. 1. Auflage, Köln: DAHTA@DIMDI 2006	Efficacy of mistletoe therapy in addition to conventional chemotherapy	The Cochrane Library, DIMDI-Superbase, Dissertation Abstracts	systematic reviews and randomised controlled trials, treatment with mistletoe ⇒ 45 publications, 5 published studies	Information from systematic reviews was insufficient to answer the research questions. The results among randomised controlled studies are inconsistent ranging from no effect on to positive effects (i.e. reduction) on chemotherapy toxicity. Mistletoe treatment in

Reference	Objective	Source of Data	Selection Criteria ⇒ N Analysed Studies (N Patients Involved)	Results
Systematic review	in malignant disease		(1,074), 2 unpublished studies (101) analysed	addition to chemotherapy has a positive effect on health-related QoL in women with breast cancer. There is no sufficient evidence to assess the effect of additional mistletoe therapy on survival or tumour remission.

AE: adverse event; CAOT: conventional adjuvant oncological therapies; QoL: quality of life; RCT: randomised controlled trial

Annex 5 AESGP list of references

Note: all literature references/study reports have already been sent earlier with the “call for scientific data” package. For convenience, the publications mentioned in the comments column have been listed below and attached here again.

EMA/322570/2011 Rev. 1: Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States.

Büssing A, Raak C, Ostermann T. Quality of Life and Related Dimensions in Cancer Patients Treated with Mistletoe Extract (Iscador): A Meta-Analysis. Evidence-Based Complementary and Alternative Medicine, Volume 2012, Article ID 219402, 8 pages. DOI: 10.1155/2012/219402.

Doehmer J, Eisenbraun J. Assessment of Extracts from Mistletoe (*Viscum album*) for Herb-Drug Interaction by Inhibition and Induction of Cytochrome P450 Activities. Phytother. Res. 2011; published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ptr.3473.

Ghelman R. Action of *Viscum album* on the pregnant albino female rat (*Rattus norvegicus albinus*, rodentia, mammalia): morphological and radiological study, Theory presented to the Federal University of Sao Paulo - Escola Paulista de Medicina for obtaining of Doctor's Title in Medicine, Sao Paulo. 2003.

Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. Cochrane Database Syst Rev 2008;(2):CD003297.

Huber R, Eisenbraun J, Miletzki B, Adler M, Scheer R, Klein R, et al. Pharmacokinetics of natural mistletoe lectins after subcutaneous injection. European Journal of Clinical Pharmacology 2010 Apr 20;1-9.

Kienle GS, Glockmann A, Schink M, Kiene H. *Viscum album* L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. Journal of Experimental & Clinical Cancer Research: CR 2009;28(1):79.

Kienle GS, Kiene H. Die Mistel in der Onkologie - Fakten und konzeptionelle Grundlagen. Stuttgart, New York: Schattauer Verlag; 2003.

Kienle GS, Kiene H. Complementary Cancer Therapy: A Systematic Review of Prospective Clinical Trials on Anthroposophic Mistletoe Extracts. Eur J Med Res 2007;12:103-19.

Kienle GS, Kiene H. Influence of *Viscum album* L (European Mistletoe) Extracts on Quality of Life in Cancer Patients: A Systematic Review of Controlled Clinical Studies. Integr Cancer Ther 2010 May 18.

Lange-Lindberg AM, Velasco Garrido M, Busse R. Misteltherapie als begleitende Behandlung zur Reduktion der Toxizität der Chemotherapie maligner Erkrankungen. GMS Health Technol Assess 2006; 2:Doc18 (20060919).

Mansky PJ, Wallerstedt DB, Sannes T, Stagl J, Johnson LL, Blackman MR, Grem JL, Swain SM, Schlodder D, Monahan BP. NCCAM/NCI phase I study of mistletoe extract and gemcitabine in patients with advanced solid tumors. *Phytomedicine* 18S, 2011 (S10-S17): S12. DOI:10.1016/j.phymed.2011.09.028.

Melzer J, Iten F, Hostanska K, Saller R. Efficacy and Safety of Mistletoe Preparations (*Viscum album*) for Patients with Cancer Diseases. *Forsch Komplementärmed* 2009;16:217-26.

Melzer J, Saller R. Lebensqualität onkologischer Patienten unter supportiver Behandlung mit *Viscum album* (parenterale Mistelpräparate). *Schweiz. Zschr. GanzheitsMedizin* 2009;21(3):157-61.

Mengs U. Toxicity of an aqueous mistletoe extract: Acute and subchronic toxicity in rats, genotoxicity *in vitro*. In: Bardocz S, Pfüller U, Pusztai A, editors. COST 98. Effects of antinutrients on the nutritional value of legume diets. Luxembourg: Office for Official Publications of the European Communities; 1998. p. 77-80.

Mengs U, Clare CB, Poiley JA. Genotoxicity testing of an aqueous mistletoe extract in vitro. *Arzneim -Forsch /Drug Res* 1997;47(3):316-9.

Nienhaus J, Leroi R. Tumorchemmung und Thymusstimulation durch Mistelpräparate. *Elemente der Naturwissenschaft* 1970;13(2):45-54.

Official German registration notification of "Bad Heilbrunner Misteltee", licensed 08th October 2009

Ostermann T, Raak C, Büssing A. Survival of cancer patients treated with mistletoe extract (Iscador): a systematic literature review. *BMC Cancer* 2009;9:451.

Rentea R, Lyon E, Hunter R. Biologic properties of Iscador: A *Viscum album* preparation. I. Hyperplasia of the thymic cortex and accelerated regeneration of hematopoietic cells following x-irradiation. *Laboratory Investigation* 1981;44(1):43-8.

Staak JO, Stoffel B, Schmidt P, Beuth J, Staak M, Pulverer G. Auswirkungen therapierelevanter Gaben Mistellektin-1 normierter Mistellextrakte auf die Organhistologie im murinen Modell. *Z Onkol* 29[4], 95-99. 1997.

"Verordnung über apothekenpflichtige und freiverkäufliche Arzneimittel", 24th November 1988 (BGBl. I S. 2150), last change 21st February 2011 (BGBl. I S. 314).

Ziegler R, Grossarth-Maticsek R. Individual Patient Data Meta-analysis of Survival and Psychosomatic Self-regulation from Published Prospective Controlled Cohort Studies for Long-term Therapy of Breast Cancer Patients with a Mistletoe Preparation (Iscador). *eCam* 2008;7(2):157-66.