EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2012
EMA/HMPC/246778/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Viscum album* L., herba

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Viscum album* L., herba
Herbal preparation(s)	• Includes: Expressed juice, ethanol extracts, wine extracts, aqueous extracts, tinctures and dry extracts [use in cardiovascular disorders]. • Includes: (Differing in terms of the manufacturing process) Fermented and unfermented aqueous extracts from leaves, stems, blossoms, sinkers and berries are used. Hosts can be apple tree (M, *Malus*), oak (Qu, *Quercus*), pine (*Pinus*), fir (*Abies*), elm (Ulmus), maple (Acer), almond (Amygdalus), birch (Betula), hawthorn (Crataegus) or ash (Fraxinus) [use in oncology].
Pharmaceutical forms	Herbal preparations in solid or liquid dosage forms for oral use [use in cardiovascular disorders] and liquid dosage forms for subcutaneous and intravenous injection [use in oncology].
Rapporteur	G. Laekeman
Assessor(s)	M. Brouckaert, G. Crauwels, D. Vandevoort

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephon☐ +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **W☐bsite** www.ema.europa.eu

Table of contents

Table of contents **2**

1. Introduction **3**

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof ..3

1.2. Information about products on the European market 4

1.3. Search and assessment methodology 8

2. Historical data on medicinal use **9**

2.1. Information on period of medicinal use in the Community 9

Cardiovascular 9

2.2. Information on traditional/current indications and specified substances/preparations .. 13

2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications 14

3. Non-Clinical Data **16**

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 16

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 18

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof 18

3.4. Overall conclusions on non-clinical data 21

4. Clinical Data **21**

4.1. Clinical Pharmacology 21

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 21

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 22

4.2. Clinical Efficacy 22

4.2.1. Dose response studies 22

4.2.2. Clinical studies (case studies and clinical trials) 22

4.2.3. Clinical studies in special populations (e.g. elderly and children) 23

4.3. Overall conclusions on clinical pharmacology and efficacy 23

5. Clinical Safety/Pharmacovigilance **23**

5.1. Overview of toxicological/safety data from clinical trials in humans 23

5.2. Patient exposure 24

5.3. Adverse events and serious adverse events and deaths 24

5.4. Laboratory findings 24

5.5. Safety in special populations and situations 24

5.6. Overall conclusions on clinical safety 25

6. Overall conclusions **25**

Annex **26**

1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Viscum album L. or European mistletoe belongs to the family of the *Loranthaceae*. It is a semi-parasitic plant. Mistletoe grows on several types of trees. The species of the host tree, the harvest time and the process of preparing the extracts determine the concentrations of the ingredients. In the pharmaceutical industry, a distinction is made between mistletoe from apple tree, oak, pine, fir, poplar, elm etc. (Hänsel *et al.* 1994).

Phytochemistry:

Mistletoe preparations contain several biologically active components: mistletoe lectins (ML I, ML II,ML III; glycoproteins with the ability to bind specifically to galactose, N-acetylgalactosamine and cell surfaces), proteins and polypeptides (in particular the viscotoxins which are composed of 46 amino acids), phenylpropanes and lignans, caffeic acid derivatives, flavonoides (especially derivatives of quercetin), biogenic amines (tyramine etc.), polysaccharides (particularly galacturonans and arabinogalactans), membrane lipids (vesicles) and other substances in low concentrations (Bisset 1994).

The presence of biologically active components and the concentrations in mistletoe extracts depends on the species of the host tree and harvest season. The difference between mistletoe lectins from fir trees and pine trees depend on the different ML III concentrations, however systematic surveys on the influence of host trees are not available. Research on lectin and viscotoxin concentrations suggests using defined organs of the plant and concrete harvesting times. Viscotoxins reach a maximum concentration in June and lectins in December (Urech *et al.* 2006).

- Herbal preparation(s)

Herbal preparations are traditionally used in two main therapeutic areas for cardiovascular disorders and in oncology. Preparations used differ in terms of the manufacturing process.
Throughout all sections of this assessment report, it is distinguished between these two main therapeutic areas abbreviated with **Cardiovascular** and **Oncology**.

Cardiovascular

Many combination products containing herbal preparations of *Viscum album* are available in Europe. A small number of mono preparations are available in Germany.

Oncology

In Europe, there are several mistletoe preparations available for subcutaneous use.

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 Viscum album preparations used in oncology.
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.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Information about products on the European market

Cardiovascular

Austria

The comminuted herbal substance is registered as THMP as herbal tea for mild cardiovascular problems. Additionally, combinations with *Allium sativum* and *Crataegus* are on the market.

In traditional medicine, mistletoe tea is recommended to normalise the blood pressure.

Czech Republic

There are two combination products:

1) *Visci albi herba, Hyperici perforati herba, Crataegi folium cum flore, Crataegi fructus, Equiseti herba, Menthae piperitae herba, Melissae hera, Matricariae flos*

2) *Visci albi herba, Crataegi folium cum flore, Crataegi fructus, Polygonii avicularis herba, Rubi fruticosi folium, Melissae herba*

Denmark

Doctors are allowed to prescribe products containing *Viscum album*.

Estonia

There is one combination product:

Hawthorn berries, St. John's worth, Milfoil, White mistletoe, Angelica, Valerian, Hop cone, Bitter-orange, Sea Salt, Sage, Rosemary, Melissa. Vitamins and minerals added.

This preparation is on the market since 30.03.2001 as a solution for oral use. Posology: 20 ml 3 to 4 times daily before meal and bedtime. Indication: fortifies heart, circulation and nerves, prevention of vitamin deficiency.

Germany

Table 1. Preparations for traditional use on the German market (see also section 2.3, Table 4)

Code	Herbal preparation	On the market since at least
1, 2, 4, 12	Visci herba: cut	1976
22, 24	Expressed juice from fresh Visci herba (1:1.60-2.20)	1976
5	Extract from fresh Visci herba with ethanol 49.3% (V/V) (1:0.45-0.55)	1976
6	Tincture from Visci herba with ethanol 26.65% (V/V) (1:5)	1976
7, 8, 16	Extract from Visci herba with liquor wine:ethanol 96% (V/V 90.5:9.5) (1:5.9)	1976
9, 10	Dry extract from Visci herba with water (4-7:1)	1976
11	Extract from Visci herba with ethanol 16% (m/m) (1:10)	1990
13	Extract from Visci herba with water (1:4.4-5.2)	1990

Code	Herbal preparation	On the market since at least
14	Tincture from Visci herba with ethanol 40% V/V (1:5)	1976
15	Expressed juice from fresh Visci herba (1:0.9-1.1)	1976
17	Expressed juice from fresh Visci herba (1:0.8-1.2)	1976
18	Tincture from Visci herba with ethanol 70% (V/V) (1:5)	1976
19	Tincture from Visci herba with ethanol 31.5% (V/V) (1:5)	1976
20	Extract from Visci herba with liquor wine (1:10)	1976
21	Extract from Visci herba with ethanol 96%:purified water:liquor wine (1.2:1:5.2 V/V) (1:5)	1976
23	Visci herba, powder	1976

Combination products

In Germany, there are 77 authorised combination products for different routes of administration.

Lithuania
Viscum album is present in multi-component homoeopathic products.

Poland
Visci herbae recentis intractum 1:1 (solvent not specified): > 30 years on the market as a liquid dosage form.

Indication: Herbal medicinal product used traditionally in patients threatened with development of arterial hypertension with suggested change of lifestyle (diet and weight loss) and under regular medical control.

Special warning: do not use in patients with arterial hypertension, treated pharmacologically.

Additional comments*:* Herba Visci has a monograph in the 'Informator Herbapol' from 1978. It is a traditional herbal medicinal product used as an aid in hypertension as herbal tea (1/2–1 spoon of *Viscum* for 1 glass of water, 2–3 times daily). It was also used in combination products for mild cardiovascular problems.

Slovak Republic
Combination product not specified.

Slovenia
Multi-component preparations (herbal tea and tincture) are on the market and traditionally used to support cardiac and circulatory functions.

Spain
More than 5 combined preparations containing *Viscum album* are on the market as authorised products.

Oncology

Austria
Preparations for parenteral use:
Several special extracts are authorised for the improvement of quality of life during or after a standard therapy of solid tumours. The kinds of tumours which are mentioned in the indication differ between the products and are based on the product specific clinical data.

Germany

There are liquid preparations for injection on the German market.

Information on Authorised Anthroposophic Medicinal Products (AMPs) in Germany containing Visci herba preparations.

Single active ingredient products:

In Germany, there are about 170 authorised single active ingredient products. They are all for subcutaneous injection (pharmaceutical form: liquid dilution for injection or solution for injection): the references of the marketed preparations date from 1978 to 1992.

At present, 5 different mistletoe product lines have marketing authorisations as anthroposophic medicinal products in Germany.

Four out of 5 manufacturers offer products at different strengths from mistletoes grown on different host trees: *Abies, Acer, Amygdalum, Betula, Crataegus, Fraxinus, Malus, Pinus, Quercus*.

Latvia

Different preparations from *Viscum* originating from *Abies, Malus* and *Pinus* are on the market.

Lithuania

Viscum album is present in multi-component homoeopathic products. Visci albi extracts are on the market as solutions for injections (host trees *Abies, Malus* and *Pinus*).

Norway

Visci albi herba is only allowed on prescription.

Visci herba can be used in cosmetics up to concentrations of 0.1%.

UK

Only mixed preparations on the market.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Combined preparations registered
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only homoeopathic products
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Combined preparations registered
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combined preparations registered
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

Member State	Regulatory Status				Comments
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations on the market: see specific comments
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations *Viscum album* not allowed in food supplements
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations on the market: see specific comments
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Homoeopathic combination products and solutions for injection
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised preparations
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify	Shampoo 0.1%
Poland	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations on the market: see specific comments
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Combined preparations registered
Slovenia	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Combined preparations registered
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combined products registered
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations submitted
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Cardiovascular

For basic information, reviews, handbooks and websites have been searched:

- Boericke, 1901 Materia Medica
- Leclerc H, 1966 Précis de Phytothérapie
- Delfosse M, 1998 Drogues végétales et Plantes médiciniales
- Duke JA, 1985 Handbook of Medicinal Herbs
- Van Hellemont J, 1985 Fytotherapeutisch Compendium
- Barnes J, 2007 Herbal Medicines
- Bisset NG. 1994 Herbal Drugs and Phytopharmaceuticals
- Hänsel K, 1994 Hagers Handbuch (Band 6)
- Rote Liste 2010-2011
- Henriettes Herbal 2011

Databases searched

- PubMed
- Cochrane
- Embase
- Journal Watch
- Internation Pharmaceutical Abstracts

Search terms

Mistletoe, Viscum album, cardiovascular, blood pressure, hypertension, traditional, adverse, events. Use (combinations made).

Oncology

Basic information has been searched in standard references

- Barnes J, Anderson LA, Philipson JD. Herbal medicines. 3rd edition. Pharmaceutical press; 2007. pp. 436-46.
- Büssing A, ed. Mistletoe. The Genus Viscum. Amsterdam: Hardwood Academic Publishers; 2000
- Hänsel R, Keller K, Rimpler H, Schneider G. editors. Hagers Handbuch der Pharmazeutischen Praxis. Berlin. Springer-Verlag; 1994. pp. 1160-79.
- Kienle, G. S., Kiene H. Die Mistel in der Onkologie. Schattauer Verlag, Stuttgart, 2003

Databases searched

- IFAEMM-data base (*Viscum album*-specific, updated monthly by systematic searches in Medline, Biosis, Embase)
- Hiscia-data base (*Viscum album* specific)
- Medline
- Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, The NHS Economic Evaluation Database, Health Technology Assess-ment Database)
- NLM Gateway.

Search terms

[(mistletoe or viscum or (mistel or mistel*) or weleda or wala or (or (mistletoe or mistletoe*) or (viscum or viscum*) or (iscador or iscador*) or (iscar or iscar*) or (helixor or helixor*) or (iscucin or iscucin*) or (isorel or isorel* or visorel or visorel*) or abnoba* or eurixor or lektinol or plenosol or aviscumine)
and
((study* or studie*) or (trial or trial*) or evaluat* or random* or investig* or (cohort* or kohort*) or outcome* or (review or review*) or (ubersicht or uebersicht or übersicht) or (uberblick or ueberblick or überblick) or (metaanalys* or meta-analys* or (meta and analys*))]

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Cardiovascular

Traditionally *Viscum album* has been used in a variety of cardiovascular disorders.

Heart
Mistletoe has been used as a cardiac tonic to treat hypertrophy with valvular insufficiency, weak or small heart pulse, failing heart compensation, inability to lie down, dyspnoea (worse lying on left side) and oedema (= dropsy) (Boericke 1976), (Henriettes Herbal 2011). A digitalis-like heart effect has been assigned to the injected cold water extract (viscotoxin) (Van Hellemont 1985). A source stated: "*… Under its use in the above named conditions the pulse becomes full, strong and regular, the cardiac dyspnea is arrested and the patient regains the ability to obtain rest in a reclining* position*. When given in large doses, it sometimes produces marked diaphoresis and it increases urine flow and bowel discharge. These results could be desirable in cases where heart problems are associated with dropsy since this combination of therapeutic action is not readily obtained in any other cardiac tonic"* (Henriettes Herbal 2011).

Other indications were irregular heart-action, palpitation during coitus and a feeling of weight, oppression (as if a hand were squeezing it) or tickling sensations about the heart (Boericke 1976). In the past, Dr. Ellingwood also advised to use *Viscum album* together with low doses of strychnine to support weak, irregular and rapid heart-action with tendency to collapse in typhoid fever (Henriettes Herbal 2011).

Blood Circulation
René Gaultier reported an effect on the central nervous system in animals when the aqueous extract was administered together with adrenaline (Leclerc 1966). Other authors report on this hypotensive

action in dogs, cats and rabbits (Henriettes Herbal 2011). The consistency of these non-clinical findings is however not robust (Delfosse 1998). Still Gaultier strongly recommended *Viscum album* in humans as an aqueous extract in doses of 0.2 g daily for the treatment of high blood pressure with arteriosclerosis and other conditions of excessive arterial tension (Henriettes Herbal 2011, Leclerc 1966). Clinical studies confirmed these recommendations (Leclerc 1966). Additionally, also symptoms accompanying hypertension such as headache, dizziness or vertigo attacks seemed to respond well (Henriettes Herbal 2011, Delfosse 1998). Because of these supposed positive effects, mistletoe is frequently used during the menopause (Delfosse 1998, Van Hellemont 1985).

Table 2. Traditional usage of mistletoe herb

Year	Source	Information about use
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 *Viscum album*
1725	Straßburger Arzneibuch (acc. to BERGER 1950)	Monograph *Viscum album*
1846	Preußische Pharmacopoe (acc. to SPAICH 1977)	Monograph *Viscum album*
1934	The British Pharmaceutical Codex	Monograph Viscum *Action and Use*: 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. *Dosage*: Mistletoe is administered as a soft extract in pills, or as an infusion or tincture (1 in 8).
1938	MADAUS	*Indication:* Reduction of blood pressure, for arteriosclerosis and hypertension, as well as dizziness. *Dosage:* 0.6-1.8 g of the stems several times daily; 1-1.5 g of the powder.
1941	Potter´s Cyclopaedia	Monograph Mistletoe, leaves. *Actions:* 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. *Dosage:* 1.9–7.8 g powdered leaves
1950	BERGER	Folia Visci. *Indications:* Hypertonia, cardiac asthma, and arteriosklerosis. Cardiac, diseases of the circulatory

Year	Source	Information about use
		system, cardiac insufficiency, dropsy, nervous states. *Dosage:* 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. *Dosage:* 2.5 g dried drug (per 1 cup cold water)
1967	Extra Pharmacopoeia, Martindale, 25. Edition	Monograph Mistletoe *Uses:* 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. *Dosage*: Mistletoe is administered as a soft extract in pills, or as an infusion or tincture (1 in 8).
1974, 1990	WEISS	Mistletoe herb is lowering the blood pressure, for mild hypertonia. 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 *Indications:* High blood pressure, arteriosclerosis, nervous tachycardia, hypertensive headache, chorea, hysteria; arterial hypertension. *Dosage:* 2-6 g dried leaves or by infusion, thrice daily. Infusion 1:20 in cold water.
1977	SPAICH	Arteriosklerosis, hypertension, dizziness, headache, excitability, neuralgia.
1979	HAGER	Monograph Herba Visci. For arthrosis, spondylosis, neuritides, chronic arthropathy; as adjuvant for hypertonia. Prophylaxis and therapy of tumours. In folk medicine for epilepsia, dizziness, amenorrhagia.
1984	WICHTL	Mistletoe herb (Visci alba herba) *Indication:* Adjuvant in hypertension, dizziness. In folk medicine for dizziness, amenorrhea, arthropathy. *Dosage:* 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.

Year	Source	Information about use
		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	*Uses:* 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 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 *Annotation:* 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	*Action:* Hypotensive
1999	DAB 1999	Monograph Mistelkraut (Visci alba herba)
1999	Martindale 32nd edition	*Uses:* Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders.
2001	VALNET	Monograph „Gui“ (*Viscum album*) *Indications:* Artheriosclerosis, hypertension and its troubles, migraine, asthma, menopause and its symptoms like palpitations, tachycardia, circulatory troubles, dyspnoe *Dosage:* 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. *Use:* 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

Year	Source	Information about use
		the anti-cancer effects are now the most important.
2010	HAGER-ROM	Monograph Visci alba herba *Use:* In folk medicine for hypertension, also epilepsia, pertussis, asthma, dizziness, amenorrhea, diarrhoea, chorea, nervous tachycardia, hysteria and nervousness. *Dosage:* 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.

The data about cardiovascular and circulatory activity have a historical character and are mainly included to demonstrate a long-lasting traditional use.

Oncology

Extracts from *Viscum album* were introduced around 1920 as an injectable in the therapy of cancer. It was introduced by Rudolf Steiner as part of a holistic and human-centred therapeutic approach within the anthroposophic medicine (Heusser 1998).

Today, mistletoe preparations are the most frequently used complementary and alternative methods (CAMs) for adjuvant treatment of cancer patients in German-speaking countries (Horneber *et al.* 2008).

2.2. Information on traditional/current indications and specified substances/preparations

Table 3. Overview of indications according to information received from the Member States

Country	Current indications
Austria	• Mild cardiovascular problems (up to 2010) • Supportive to general measures in order to improve quality of life in case of solid tumours during and after standard therapy (*unterstützend zu allgemeinen Maßnahmen zur Verbesserung der Lebensqualität bei soliden Tumoren während und nach einer Standardtherapie*)
Czech Republic	Mixtures: no further details about indications provided
Denmark	Only prescribed for specific indications
Estonia	• For fortification of heart, circulation and nerves. • Combination with vitamins: prevention of vitamin deficiency
Germany	• Diverse cardiovascular indications • Adjuvant in cancer treatment • Supportive for condition and integration in order to counter the indepent cell growth *("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;*

Country	Current indications
	zur Rezidivprophylaxe nach Geschwulstoperationen.“)
Latvia	Anthroposophic herbal medicine for the adjunctive therapy in malignant disease
Lithuania	Complementary therapy in malignant diseases for the improvement of quality of life and possibly the course of the disease
Norway	No specific indications communicated
Poland	• Used traditionally in patients threatened with development of arterial hypertension with suggested change of lifestyle (diet and weight loss) and under regular medical control • A solution for injections is an anthroposophic medicine. According to anthroposophic knowledge of man and nature, It 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 *(“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*).”
Slovak Republic	No specific indications communicated
Slovenia	Traditionally used to support cardiac and circulatory functions
Spain	No specific indications communicated

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Cardiovascular

Estonia

Hawthorn berries, St. John’s worth, Milfoil, White mistletoe, Angelica, Valerian, Hop cone, Bitter-orange, Sea Salt, Sage, Rosemary, Melissa. Vitamins and minerals added.

This preparation is on the market since 30.03.2001 as a solution for oral use. Posology: 20 ml 3 to 4 times a day before meal and bedtime. Indication: fortifies heart, circulation and nerves, prevention of vitamin deficiency.

Germany

Table 4. Practical information on preparations traditionally used to support the circulatory function (see also section 1.2, Table 1)

Code	Pharmaceutical form	Posology: all posologies are intended for adults and adolescents > 12 years
1	Herbal tea	2-3 x daily 1 cup of tea Put 1 tea-bag (= 2 g) in 1 cup full of cold water, extract 1-2 h and stir occasionally, remove the tea-bag and heat shortly until boiling. Let the

Code	Pharmaceutical form	Posology: all posologies are intended for adults and adolescents > 12 years
		tea cool down to drinking temperature and then drink it.
2	Herbal tea	2-3 x daily 1 cup of tea 1 tea-bag (= 2 g) in 1 cup of boiling water, extraction time 5-10 min
3	Oral liquid	2 x daily 5-10 ml liquid containing 100% expressed juice
4	Herbal tea	2 x daily (in the morning and in the evening) 1 cup of tea 1 tea-bag (= 2 g) in 150 ml of boiling water, extraction time 5 min
5	Oral liquid	3 x daily 20-30 drops (25 drops = 1 ml) The daily dose can also be divided in two single doses
6	Oral liquid	3 x daily 10-20 drops containing 100% tincture (17 drops = 1 ml)
7	Oral liquid	2-3 x daily 15-20 drops
8	Oral liquid	2-3 x daily 15-20 drops
9	Coated tablet	1 x daily 2-3 containing 300 mg extract each
10	Coated tablet	2-3 x daily 1-2 containing 150 mg extract each
11	Oral liquid	3 x daily 15 ml liquid
12	Herbal tea	2-3 x daily 1 cup of tea Put 1 tea-bag (= 2 g) in 1 cup full of cold water, extract 1-2 h and stir occasionally, remove the tea-bag and heat shortly until boiling. Let the tea cool down to drinking temperature before use
13	Oral liquid	3-4 x daily 10 ml liquid
14	Oral liquid	3 x daily 20-30 drops
15	Oral liquid	3 x daily 50 drops (17 drops = 1 ml = 1g). 100 g liquid contain 83.3 g expressed juice
16	Oral liquid	2-3 x daily 15-20 drops
17	Oral liquid	2-3 x daily 15 ml liquid containing 100% expressed juice
18	Oral liquid	3 x daily 20-25 drops containing 100% tincture (25 drops = 1 g)
19	Oral liquid	3 x daily 30 drops containing 100% tincture
20	Oral liquid	2-3 x daily 20 ml liquid 20 ml liquid contain 18.6 g extract
21	Oral liquid	3-4 x daily 30-40 drops (32 drops = 1 ml)
22	Oral liquid	3 x daily 10 ml liquid containing 100% expressed juice
23	Coated tablet	3-4 x daily 1 containing 190 mg powder
24	Oral liquid	3 x daily 10-20 ml liquid containing 100% expressed juice

Posology according to reference sources

- **dried leaves**: 2-6 g as an infusion 3 times per day (Barnes *et al.* 2007)
- **herba visci**: 1 to 3.8 g (2 teaspoons or 1 tablespoon) in a cup with cold water. Let stand for 10-12 hours (one night), filter and drink (1-2 cups per day on an empty stomach, for the treatment of hypersensitivity) (Henriettes Herbal 2011, Leclerc 1966, Delfosse 1998, Van Hellemont 1985).
- **liquid extract**: 25 drops per dose; multiple times per day (Henriettes Herbal 2011), (Delfosse 1998), (Van Hellemont 1985); 1-3 mL (1:1 in 25% alcohol) 3 times per day (Barnes *et al.* 2007)
- **infusion**: 40-120 ml (1:20 in cold water) daily (Barnes *et al.* 2007)

- **mother tincture**: 3 times 30 drops daily (Delfosse 1998), (Van Hellemont 1985); 0.5 ml (1:5 in 45% alcohol) 3 times per day (Barnes *et al.* 2007)

- **syrup** (containing 0.3 to 0.5 g watery extract on 200 g syrup simplex): 0.02 to 0.05 g extract per day (Henriettes Herbal 2011, Leclerc 1966)

Particulars

- *Viscum album* is heat sensitive, so extracts are best prepared cold (Delfosse 1998, Van Hellemont 1985)
- Oral intake and long-term use are free of toxic side-effects (Delfosse 1998, Van Hellemont 1985)

- If sedation occurs, the doses must be diminished (Henriettes Herbal 2011)

- Preparations of the fresh plant should be used, as the drug loses its properties when old (Henriettes Herbal 2011)

- According to Nicolline a maceration with white wine is more active and most likely the original way of preparing *Viscum album* extracts (40 g fresh cut plant, 1000 g white wine; 130 g taken daily)(Leclerc 1966).

Oncology

Additional information on cancer treatment (Rote Liste 2010 & 2011)[1]: for all preparations' doses are individualised to the patient.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Cardiovascular

Cardiovascular effects

Many studies concerning the hypotensive action of *Viscum album* were conducted between 1907 and 1958. Parenteral application of extracts was nearly always accompanied with cardiotoxicity. An example is a study in dogs where a cold-water mistletoe extract was administered intravenously and resulted in a cardiotoxicity and respiratory depression. By heating the extract, it is possible to circumvent the toxic effect while preserving the hypotensive action (Hänsel *et al.* 1994).

A study in rats over a period of 2 weeks resulted in a blood pressure decrease of 30% in healthy animals and 38% in hypertensive rats (after 4 weeks even up until 58%). Researchers administered an aqueous extract prepared from the fresh plant through a gastric tube in a dosage equivalent to 10 times the therapeutic dose (= 0.4 ml/kg). An influence on the coronary and peripheral vessels was not seen (Hänsel *et al.* 1994).

Some compounds of *Viscum* were reported to demonstrate vascular effects.
Rat aortic noradrenaline-contracted rings were used as an experimental model. Vascular effects of phenolic compounds and subfractions isolated from the n-butanolic fraction of *Viscum album* were used. Some of the compounds caused concentration-dependent contractions. This was the case for

[1] Rote Liste 2010 (this publication is published by an industrial organization; it does not give a complete marketing overview)

syringin and coniferin. Only one compound (Kalopanaxin D) displayed a very slight relaxant response. Also less polar subfractions had a weak-concentration-dependent relaxing effect (Delloman *et al.* 2000).

One study indicates that after consecutive administration of a mistletoe fluid extract (not further specified) at 0.5 ml/kg, 1 ml/kg and 2 ml/kg daily in spontaneous hypertensive rats for 14 days, the blood pressure slowly reduced, lasting a long period and with a significant dose-effect relation (Ye *et al.* 2009).

Influence on insulin secretion

Some insulin-secreting activity was reported for *Viscum*.

The model used was a cell culture of cloned pancreatic B-cells. In acute 20-min tests, 1-10 mg/ml aqueous extracts of mistletoe (no further details given) evoked a stepwise 1.1- to 12.2-fold stimulation of insulin secretion. This effect was abolished by 0.5 mM dizoxide. The insulin releasing effect of mistletoe extract was unaltered by 16.7 mM glucose, L-alanine ’10 mM), 3-isobutyl-1-methylxanthine (IBMX) (1 mM) or a depolarizing concentration of KCl (25 mM).

The activity of the extract was not abolished by heat during extract preparation. It was not mediated by lectine (Gray and Flatt, 1999).

Oncology

The spectrum of active *Viscum album* constituents is broad. Kienle & Kiene (2003) and Tabiasco *et al.* (2002) reported on cytotoxic and immunomodulatory properties of lectins and viscotoxins. These investigations are not further commented as the oncological use of *Viscum* 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 (see section 4.3).”

Assessor’s overall conclusions on pharmacology

Cardiovascular

Some experimental evidence for a blood pressure lowering effect can be deduced from preclinical investigations. Studies were done with (hypertensive) rats and dogs. More information is needed about the exact nature of the extracts used. Parenteral administration of water extracts leads to toxic effects in dogs. Oral administration to normal and hypertensive rats and dogs lowered the blood pressure in a dose-dependent way.

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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Cardiovascular

No data are available on orally administered *Viscum* preparations.

Oncology

Data on pharmacokinetics are limited to *in vitro* studies.

3.3. Overview of available toxicological data regarding the herbal substance(s) / herbal preparation(s) and constituents thereof

An overview of lethal doses as summarised from different sources by Kienle & Kiene (2003) is tabled below. Preclinical toxicological data are limited and mostly not related to the preparations used in humans.

Table 5. LD_{50} scores overview (Kienle & Kiene 2003)
LD50 of *Viscum* extracts, lectines, viscotoxines and polysaccharides

Viscum extract (Iscador M®)	700 mg/kg in CD-I albinomice (i.p.) 348 mg/kg in C57/BL6 mice (i.p.) 378 mg/kg in Sprague-Dawley rats (i.p.) 276 mg/kg in Swiss mice (i.p.) 168 mg fresh plant material/kg in BL6-mice (application route unclear)
Viscum extract (Iscador Q®)	500 mg/kg in mice (i.v.) 1200 mg/kg in mice (s.c.)
Viscum juice	$\pm$32 mg/kg in mice (i.p.)
Viscum lectines ML I	28 mg/kg in mice (i.p.)
Viscum lectines ML II	1.5 mg/kg in mice (i.p.)
Viscum lectines ML III	55 mg/kg in mice (i.p.)
Viscotoxins	0.5 mg/kg in mice (i.p.) 0.1 mg/kg in mice (i.v.)
Viscum polysaccharides	>2.25 g/kg in mice (i.p.)

i.p.= intraperitoneally
i.v.= intravenously
s.c.= subcutaneously

The precise cause of in-vivo toxicity is still unclear and probably not a consequence of the direct cytotoxicity. Cytokine production and haemagglutinating activity however could be involved. In all cases, intravenous and intracardial injections were found more toxic than the intraperitoneal, subcutaneous or intramuscular administrations (Stein 2000).

Oral ingestion

Viscum album can be considered as non-toxic following oral ingestion. Nausea, vomiting, diarrhoea, hypertension followed by shock have been described in very few cases, especially after ingestion of the berries. A chronic toxicity is not known. Oral mistletoe preparations are mainly used to treat hypertension (Kienle & Kiene 2003).

Acute toxicity

Cardiovascular

No data on preparations used orally.

Oncology

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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

Chronic toxicity

Cardiovascular

No data on preparations used orally.

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 currently not possible because some essential criteria are not fulfilled (see section 4.3).

Genotoxicity

Cardiovascular

No data on preparations used orally.

Oncology

Specific oncological preparations were tested for mutagenic effects in the Ames test and a micronucleus test (Mengs *et al*. 1997, 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

Reproduction

Cardiovascular

No data on preparations used orally.

Oncology

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. The evaluation with respect to well-established use is currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

Assessor's overall conclusions on toxicology

In animal toxicity of *Viscum album* extracts was assessed as very low. 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. The evaluation with

respect to well-established use is currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

3.4. Overall conclusions on non-clinical data

Cardiovascular

Some experimental evidence for a dose-dependent blood pressure lowering effect is coming from preclinical investigations with *Viscum* extracts. Studies were done with (hypertensive) rats and dogs.

No data on pharmacokinetics on orally administered preparations are available.

LD_{50} values have been quantified for mistletoe lectins and viscotoxins. However, extrapolation to possible toxicity or safety of herbal preparations for human use remains difficult.

Oncology

Different *Viscum* preparations have been tested in experimental *in vitro* as well as *in vivo* models. No further details are given as the subcutaneous use of *Viscum* 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Cardiovascular

Some authors reported on the use of *Viscum album* in hypertension and arteriosclerosis. Henri Busquet concluded that the hypotensive action is not due to a weakening effect on the heart but rather on the blood vessels (anti-spasm) (Henriettes Herbal 2011, Leclerc 1966). After injection of the extract, A. Jarish and C. Heuze found vasodilatation of liver vessels. Also Arnold Holste showed a very strong influence of the extract on arterioles and capillaries (Leclerc 1966).

The hypotensive effect documented for mistletoe has been in part attributed to various biologically active constituents such as choline esters (acetylcholine), histamine, gamma-aminobutyric acid (GABA), tyramine and flavones (Henriettes Herbal 2011, Duke 1985, Barnes *et al.* 2007). These substances probably stimulate the parasympathetic nervous system causing a dilatation of the blood vessels (Van Hellemont 1985). Some authors however, doubt the anti-hypertensive action after oral administration. Others see a reduction of 20% of arterial hypertension cases and in many an improvement of the subjective complaint (e.g. headache, dizziness and unspecific pain in the heart area) (Van Hellemont 1985). The exact mechanism of the hypotensive effect is unclear, maybe an inhibitory action on the excitability of the vasomotor centre in the medulla oblongata is in play. The highest activity has been reported for mistletoe leaves parasitising on willow (Barnes *et al.* 2007).

A normalising effect not only on hypertensive but also on hypotensive states has been described (Barnes *et al.* 2007). Other reported indications are haemorrhage and varicose veins (Duke 1985).

Oncology

See sections 4.1.2–4.3.

Assessor's overall conclusions on pharmacodynamics

Cardiovascular

The hypotensive effect described for mistletoe has been partially attributed to various biologically active constituents such as choline esters (acetylcholine), histamine, gamma-aminobutyric acid (GABA), tyramine and flavones. The extract has apparently an anti-spasmodic effect on the blood vessels due to parasympatic stimulation. However, the exact mode of action is still unknown.

A normalising effect not only on hypertensive but also on hypotensive states has been described. Other reported indications are haemorrhage and varicose veins.

Oncology

See sections 4.1.2–4.3.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Cardiovascular

No data available.

Oncology

Data on pharmacokinetics are limited.

Schöffski *et al.* (2004; 2005) did a pharmacokinetic evaluation on recombinant *Viscum* lectin analogues. Huber *et al*. (2010) did a human pharmacokinetic investigation with a complete plant extract. No further details are included in this assessment report, as they are related to an oncological use of *Viscum* 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 (see section 4.3).

4.2. Clinical Efficacy

4.2.1. Dose response studies

Dose response studies are not available.

4.2.2. Clinical studies (case studies and clinical trials)

Cardiovascular

An orally taken dose of 1 g powder per day resulted, after a period of 7 to 14 days, in a blood pressure decrease until normal values which in some cases was still preserved for several months after treatment stop. Headaches, black spots in vision attacks of vertigo and other signs of hypertension disappeared after 3 to 5 days of therapy (Hänsel *et al.* 1994).

An open study in 120 patients (ranging 18 to 75 years old) with light to moderate hypertension (WHO grade I-II) resulted in an average blood pressure decrease from 165 to 150 mmHg systolic in rest and from 187 to 180 mmHg systolic pressure during physical exercise after 6 weeks mistletoe therapy (drops, juice, tablets; correspondingly 0.6-2.8 g daily). Subjective symptoms (general well-being, headache, dizziness, fatigue) showed a tendency to improvement (Hänsel *et al.* 1994). Other research revealed similar results, although some authors disagree (Henriettes Herbal 2011, Wichtl 1994, Hänsel

et al. 1994). Lowering of blood pressure is of short duration and may be preceded by a rise. It is therefore concluded that the drug is not clinically useful for this purpose (Henriettes Herbal 2011).

Oncology

Lange-Lindberg *et al.* (2006) made a health technology assessment of *Viscum album* preparations in Germany. Since then additional reviews and meta-analysis have been published of Clinical Trials with Mistletoe Therapy in Cancer Patients (Kienle & Kiene 2007; Horneber *et al*. 2008; Ziegler & Grossarth-Maticek 2010; Kienle *et al*. 2009; Melzer *et al*. 2009; Melzer & Saller 2009; Osterman *et al*. 2009; Kienle & Kiene 2010; Bussing *et al*. 2012).

Convincing blinded randomised controlled trials 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

4.2.3. Clinical studies in special populations (e.g. elderly and children)

Chernyshov *et al.* (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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

4.3. Overall conclusions on clinical pharmacology and efficacy

Cardiovascular

There is little evidence for a blood pressure lowering effect of mistletoe preparations. The number of patients is limited and the inclusion criteria are not very well defined. Different preparations were used in combination with other substances or without further specification. The results of clinical observations are scarce and rather conflicting.

Oncology

The evaluation of herbal medicines with *Viscum album* with respect to the well-established use is not possible because some essential criteria for evaluation are not fulfilled:

- The method of production of some of the extracts is currently not 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.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

Studies available in the public domain have been carried out with cancer patients (Hamre *et al.* 2006; Stoss *et al.* 1999; Horneber *et al.* 2008; Goebell *et al.* 2002; Kleeberg *et al.* 2004; Piao *et al.* 2004; Semiglasov *et al.* 2004; Semiglasov *et al.* 2006; Steuer-Vogt *et al.* 2001). These studies are not evaluated as the scope of the legislation on traditional herbal medicinal products does not cover the parenteral treatment of cancer. The therapeutic use of *Viscum album* in cancer therapy is different from the regulatory framework applicable to traditional herbal medicinal products laid down in Chapter

2a of Directive 2001/83/EC as amended, and in particular Article 16a(1)(a) on their use in minor indications that do not require supervision of a medical practitioner.

The evaluation with respect to well-established use is not possible because some essential criteria are not fulfilled (see section 4.3).

5.2. Patient exposure

See clinical studies (section 4).

5.3. Adverse events and serious adverse events and deaths

Cardiovascular

No specific clinical investigations on human safety have been carried out.

Oncology

No further details are included in this assessment report, as they are related to an oncological use of *Viscum* 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

5.4. Laboratory findings

Not applicable.

5.5. Safety in special populations and situations

Intrinsic (including elderly and children) / extrinsic factors

Cardiovascular

No specific studies have been carried out in special populations.

Oncology

There is only limited experience in children.

Drug interactions

Drug interactions seem rather unlikely according to studies *in vitro* (Doehmer *et al.* 2012) and clinical investigations (Mansky *et al.* 2011) conducted with various mistletoe preparations.

Use in pregnancy and lactation

The use of *Viscum album* preparations is not recommended during pregnancy and breastfeeding because of its possible content on lectins and viscotoxins (Barnes *et al.* 2007).

Overdose

Not reported.

Drug abuse

Not relevant.

Withdrawal and rebound

Not reported.

Effects on ability to drive or operate machinery or impairment of mental ability

Not reported.

5.6. Overall conclusions on clinical safety

Cardiovascular

The safety of *Viscum album* preparations is not intentionally studied.

Oncology

No analysis was made because oncological use of *Viscum album* 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

6. Overall conclusions

There is no monograph on Mistletoe in the European Pharmacopoeia. As mistletoe can grow and be harvested on several host trees, the origin of the herbal substance can vary. It is not clear what could be the consequences for the human therapeutic use.

Cardiovascular

Mistletoe preparations can lower the blood pressure in (hypertensive) rats and dogs in a dose-dependent way. Some of the experiments are outdated and the practical circumstances of the interventions and outcomes are not always clearly communicated.

No data about pharmacokinetics on orally administered preparations are available.

LD50 –values of mistletoe lectins and viscotoxin have been quantified.

No adequate data on genotoxicity of different herbal preparations are available.

Viscum album preparations are traditionally used in some European countries for mild cardiovascular disorders. There is no evidence of clinical efficacy and a well-established use indication cannot be supported.

The 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” is not fulfilled.

Oncology

No analysis was made because oncological use of *Viscum album* 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 currently not possible because some essential criteria for evaluation are not fulfilled (see section 4.3).

More particularly the following requirements are not fulfilled.

The 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"

The requirement laid down in Article 16a(1)(b) of Directive 2001/83/EC that the herbal substance or herbal preparation is "exclusively for administration in accordance with a specified strength and posology".

The requirement laid down in Article 16a(1)(c) of Directive 2001/83/EC that the herbal preparation is an oral, external and/or inhalation" preparation.

Furthermore the evaluation of herbal medicines with *Viscum album* with respect to well-established therapeutic use is not possible because some essential criteria for evaluation are not fulfilled:

- The method of production for some of the extracts is not always 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.

CONCLUSION

The current situation does not allow the preparation of a monograph for *Viscum album* according to the standard procedures based on Directive 2001/83/EC.

Annex

List of references