EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Viscum album* L., herba
Herbal preparation(s)	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), oak (Qu), pine (P), or elm (U) [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].
Pharmaceutical forms	Herbal preparations in solid or liquid dosage forms for oral use and liquid dosage forms for subcutaneous injection.

Note: This draft Assessment Report is published to support the release for public consultation of the draft Public statement on *Viscum album* L., herba. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the public statement. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft public statement.

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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

Not applicable.1.2. Information about the products on the European market 3

1.2. Information about the products on the European market 4

1.3. Search and assessment methodology 7

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 . 10

2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications 11

3. Non-Clinical Data **13**

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 13

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 14

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof 14

3.4. Overall conclusions on non-clinical data 16

4. Clinical Data **16**

4.1. Clinical Pharmacology 16

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 16

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents 17

4.2. Clinical Efficacy 17

4.2.1. Dose response studies 17

4.2.2. Clinical studies (case studies and clinical trials) 18

4.2.3. Clinical studies in special populations (e.g. elderly and children) 18

4.3. Overall conclusions on clinical pharmacology and efficacy 18

5. Clinical Safety/Pharmacovigilance **19**

5.1. Overview of toxicological/safety data from clinical trials in humans 19

5.2. Patient exposure 19

5.3. Adverse events and serious adverse events and deaths 19

5.4. Laboratory findings 19

5.5. Safety in special populations and situations 19

5.6. Overall conclusions on clinical safety 20

6. Overall conclusions **20**

Annex **21**

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, fir, poplar etc. (Keller *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 of lectin and viscotoxin concentrations suggests using defined organs of the plant and concrete harvesting times. Viscotoxins reach a maximal 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.

- 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 the 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

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
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

CODE	HERBAL PREPARATION	On the market since at least
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 multicomponent 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
Combinational product is 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 Anthroposophical Medicinal Products (AMPs) in Germany containing Visci herba preparations:

In total in Germany there are 204 authorised AMPs containing Visci herba preparations.

Single active ingredient products:
In Germany, there are 127 authorised single active ingredient products. They are all for subcutaneous injection (pharmaceutical form: liquid dilution for injection or solution for injection): ABNOBAviscum® (oldest references dates from 1990), Cefalektin® (no reference date), Eurixor® (oldest reference dates from 1992), Helixor® (oldest reference dates from 1985), Iscador® (oldest reference dates from 1986), Isucin-Viscum® (oldest reference dates from 1990), Isorel® or Vysorel® (oldest reference dates from 1990), Lektinol® (no reference date).

Lithuania
Viscum album is present in multicomponent homoeopathic products. Visci albi extracts are on the market as solutions for injections (Helixor A, M, P).

Norway
Visci albi herba is only allowed on prescription.

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

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
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

Member State	Regulatory Status				Comments
					Viscum album not allowed in food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
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:	Not known
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:	No authorised preparations

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
- Keller 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
- Keller K, Hänsel R, 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 ple-nosol 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 ue-berblick OR überblick) OR (metaanalys* OR meta-analys* OR (meta AND analys*))]

Inclusion/Exclusion Criteria:

Inclusion Criteria:

- Clinical studies & Reviews: all designs published between 2006-2010
- Intervention: *Viscum album* / mistletoe (applied alone or in combination with other therapies)
- Population: patients with *all* diseases, healthy people
- Outcome: clinical relevant outcomes, safety outcomes
- Language: all languages.
- Published and not published

Exclusion Criteria:

- No inclusion criteria
- Single case reports*, no statistical analysis, no systematic data acquisition
- Qualitative studies
- Studies not finished, no interim analysis available
- Studies not published and no data available
- Severe deficiencies in methodology or presentation that makes analysis impossible
- Studies only describing immunologic parameters

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 nerve system in animals when the watery extract was

administered together with adrenaline (Leclerc 1966). Also 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 a watery 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 positive effects, mistletoe is frequently used during the menopause (Delfosse 1998), (Van Hellemont 1985).

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 anthroposophical medicine (Heusser 1998). This medicinal approach is rooted in a philosophy which considers disease not as an isolated process but sees it rather as part of the human existence. It focuses on promoting the self-healing properties of the patient in dialogue with a conventional western approach. It is said that through the formative forces and common elements in nature, one tries to find a relationship between the mineral kingdom, the plant kingdom, the animal kingdom and human beings. Disease occurs when these forces are disharmonized within the human constitution. By using substances from nature as a cure for humans, anthroposophical medicine tries to re-establish harmony and expel the disease. As such, *Viscum album* treatment tries to balance the distorted human state responsible for the cancer to develop. Preparations classified as antroposophical are: abnobaVISCUM®, Helixor®, Iscador®, Iscucin® and Isorel®.

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

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

Table 2. Overview of indications according to information received from the Member States

COUNTRY	CURRENT INDICATIONS
Austria	Mild cardiovascular problems (up to 2010)
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[1]
Lithuania	Adjuvant therapy in cancer
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
Slovak Republic	No specific indications communicated
Slovenia	Traditionally used to support cardiac and circulatory functions
Spain	No specific indications communicated

[1] Rote Liste 2010 (published by an industrial organization; does not give a complete market overview).

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 3. Practical information on preparations traditionally used to support the circulatory function (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 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 and then drink it
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

CODE	PHARMACEUTICAL FORM	POSOLOGY: all posologies are intended for adults and adolescents > 12 years
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)[2]: for all preparations' doses are individualised to the patient.

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

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 (Keller *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 (Keller *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 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).

Experiments were done with spontaneous hypertensive rats (SHR) and renal hypertensive dogs (RHD) to investigate the effect of compound mistletoe extract (fufang jisheng luijin gao). The animals received the extract in single doses and daily doses during 14 days. Both single doses and a 14-day consecutive administration of the mistletoe extract significantly lowered blood pressure. A dose-effect relationship could be seen.

Results indicate that after consecutive administration of the mistletoe fluid extract at 0.5 ml/kg, 1 ml/kg and 2 ml/kg every day 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).

	Dose (mL/kg)	**Effective cases**	**Effective rate**	**Reduced value and range of systolic blood pressure**
Control		0	0	0±0.800 – 2.93±0.667
Extract	0.5	7	60*	-1.598±0.800 – -2.94±0.800
Extract	1.0	9	80.2**	-0.671±0.899 – -2.78±1.39
Extract	2.0	12	100**	1.330±1.330 – -3.33±1.07
Bezoar Hypertension-relieving Pills	0.4 g/kg	7	70**	0.133±0.800 – -3.60±1.60

Notes: A reduction of 1.33 kPa in spontaneous hypertensive rats was regarded as effective; Compared with the control group, *P<0.05, **P<0.01

Influence on insulin secretion

Some insulin-secreting activity was seen with *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) report 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.

Assessor’s overall conclusions on pharmacology

CARDIOVASCULAR

Some experimental evidence for a blood pressure lowering effect is coming 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 lead 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.

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 is tabled below. Preclinical toxicological data are limited and mostly not related to the preparations used in humans.

LD_{50} scores overview (Kienle & Kiene 2003)

Substance	**LD_{50}**	
Viscum album expressed juice	± 32 mg/kg mouse (ip)	
ML I	28.6 µg/kg mouse (route of application is unclear)	28 µg/kg (ip)
ML II	46.7 µg/kg mouse (route of application is unclear)	1.5 µg/kg (ip)
ML III		55 µg/kg (ip)
Viscotoxin	0.5 mg/kg mouse (ip)	0.1 mg/kg mouse (iv)
Polysaccharide fraction	> 2.25 g/kg mouse (ip)	

The precise cause of death is still unclear and probably not a consequence of generalised cell injury. Cytokine production and haemaggluninating 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 human data available.

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.

Chronic toxicity

Unknown

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 (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.

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.

Assessor's overall conclusions on toxicology

In animal tests toxicity of *Viscum album* 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.

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.

Toxicity of mistletoe lectins and viscotoxin could be quantified.

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.

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 used *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). Kochmann isolated an acetylcholine like parasympatic irritant from mistletoe plants growing on apple trees. Its action was influenced by atropine and the substance established a reduction in blood pressure after oral intake (Henriettes Herbal 2011). 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 hemorrhage and varicose veins (Duke 1985).

ONCOLOGY

See sections 4.1.2–4.3.

Assessor's overall conclusions on pharmacodynamics

CARDIOVASCULAR

The hypotensive effect documented 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 hemorrhage 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) and Huber *et al.* (2010) did a pharmacokinetic evaluation on recombinant *Viscum* lectin analogues. 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.

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 (Keller *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 and from 187 to 180 mmHg diastolic pressure after 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 (Keller *et al.* 1994). Other research revealed similar results, although some authors disagree (Henriettes Herbal 2011), (Wichtl 1994), (Keller *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. Convincing blinded randomised controlled trails 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.

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.

4.3. Overall conclusions on clinical pharmacology and efficacy

CARDIOVASCULAR

There is little evidence for a blood 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 the extracts is not in the public domain.
- The qualitative and quantitative composition of the extracts used in clinical studies is not known and will depend on the host plant.
- Standard posologies could not be derived from the clinical studies.

5. Clinical Safety/Pharmacovigilance

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

The studies available in the public domain are carried out with cancer patients. These studies are not evaluated as the scope of traditional herbal medicine does not cover the parenteral treatment of cancer (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). 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

Safe use is recommended in adults and elderly only (see clinical studies).

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.

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

Caution must be taken in consideration of potential interactions of *Viscum album* extracts and other components with similar or opposing effects (Barnes *et al.* 2007).

Use in pregnancy and lactation

Use of *Viscum album* preparations is not recommended during pregnancy and breastfeeding because of its toxic constituents (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.

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.

Acute toxicity of mistletoe lectins and viscotoxin could be quantified, while more data on genotoxicity of different herbal preparations should be gathered.

Viscum album preparations are traditionally used in some European countries for cardiovascular disorders. The HMPC concluded that these indications are not suitable for self medication with traditional herbal medicinal products. There is also no evidence of clinical efficacy and a well-established use indication is not supported.

ONCOLOGY

With regard to the use of *Viscum album* in cancer therapy, it is concluded that this is outside the scope of the Directive 2001/83/EC as amended for traditional herbal medicinal products.

It is also concluded that with respect to the use in cancer therapy, the information available in the public domain was not sufficient to enable a well-established use indication to be supported.

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 of the extracts is not in the public domain.
- The qualitative and quantitative composition of the extracts used in clinical studies is not known and will depend on the host plant.
- Standard posologies could not 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.

Annex

List of references