

RECOMMENDATIONS FOR USE



ABNOBA **VIScum**[®]

Information for Healthcare Professionals

OVERVIEW

How to reach optimal dosage
and long-term therapy

ABNOBA **VISCUM**[®]

Start of treatment and how to reach optimal dosage (short protocol)

Treatment starts with

**abnobaVISCUM 0.02 mg, 1 ml (= 1 ampoule)
3 x per week s.c. over 2½ weeks – total of 8 ampoules (= 1 package)**

Any of the reactions 1 – 3 indicate that the dosage is correct:

- 1 Local inflammatory reaction at the injection site up to $\varnothing = 5$ cm.
- 2 Temporary body temperature increase of 0.5 - 1.0 °C within 12 hours following the injection.
- 3 Patient experiences changes in condition: pain relief, deeper sleep, better appetite.

Reactions 1 and 2 decrease in intensity after 2½ weeks (if not, administer 0.02 mg for an additional 2½ weeks). Thereafter dosage can be increased to the next strength.

The symptoms of fatigue, mild shivering, general malaise, headaches and transient dizziness that can arise on an injection day are signs of a correct dosage, as long as these reactions subside within the following day.

Weeks 1 - 3

Example:
Week 1 Mon. Wed. Fri.
Week 2 Mon. Wed. Fri.
Week 3 Mon. Wed.

**abnobaVISCUM 0.2 mg, 1 ml (= 1 ampoule)
3 x per week s.c. over 2½ weeks – total of 8 ampoules (= 1 package)**

Reactions 1 – 3 (above) will regularly reappear. If reactions are too strong or severe, please follow the recommendations of how to proceed in case of too high dosage or overdosage (see adjacent page).

Weeks 3 - 6

Either: If well-tolerated and the intensity of reactions 1 – 3 subside again, and if the patient's general condition is good, dosage can again be increased to the next higher strength:

**abnobaVISCUM 2 mg, 1 ml (= 1 ampoule)
Maintain s.c. inj. 3 x per week, continue with this strength as long-term therapy.**

Thus the individual optimal dosage for long-term therapy has been reached.

Or: In cases of poor general condition or if the patient responds very sensitive, the dosage already reached should be maintained.

**abnobaVISCUM 0.2 mg, 1 ml (= 1 ampoule)
Maintain s.c. inj. 3 x per week, continue with this strength as long-term therapy.**

Thus the individual optimal dosage for long-term therapy has been reached.

Dosage is too high when: *

- the local inflammatory reaction is larger than 5 cm \varnothing and smaller than 10 cm \varnothing :
→ reduce injection volume to 0.5 ml (½ ampoule) for the next 3 injections
- the local inflammatory reaction is larger than 10 cm \varnothing :
→ inject the next lowest strength for 2½ weeks (8 ampoules)
- there is persistent weakness, nausea and / or dizziness:
→ inject the next lowest strength for 2½ weeks (8 ampoules)

Severe reactions and side effects with 0.02 mg persist:

Continue treatment with 8 ampoules of abnobaVISCUM potency D6 of the same host tree.

Long-term therapy

Once the individual optimal dosage has been reached, from week 6 onwards the following course is often applied:

S.c. injections are maintained at 3 x per week for up to 2 years. Then 2 x per week for another year. After 3 years, treatment-free intervals of 3 months can be introduced.

In special cases the doctor can decide during the therapy to increase the dosage to 20 mg.

CAUTION:

Following a treatment-free interval lasting longer than 4 weeks, treatment should always start again with a lower dosage (0.02 mg).

* A detailed description can be found in the English version of the SmPC, the Recommendations for Use of abnobaVISCUM, and on the homepage www.abnoba.de in the area for professionals.

Choosing the sort of preparation (i.e. host tree)

Tumours without metastatic spread and precanceroses

Tumour Localisation	ABNOBAVISCUM [*]	Examples
Gastrointestinal Tumours	Quercus or Pini	Gall Bladder Carcinoma Colon Carcinoma Gastric Carcinoma Pancreatic Carcinoma Rectal Carcinoma
Bronchial Carcinoma	Abietis or Aceris	Bronchial Carcinoma Pleural Mesothelioma
Gynaecological Tumours	Mali or Abietis	Breast Cancer Ovarian Carcinoma Uterine Carcinoma Cervical Carcinoma
Urogenital Tumours	male: Crataegi or Quercus female: Mali or Pini	Bladder Carcinoma Testicular Carcinoma Renal Cell Carcinoma Carcinoma of the Prostate
Cutaneous Tumours	Abietis or Betulae	Melanoma
Otorhinolaryngologic Tumours	Abietis or Amygdali	Carcinoma of the oral cavity Tounge Carcinoma
Central Nervous System Tumours	Abietis or Betulae	Glioblastoma
Sarcoma / Bone and Soft Tissue Tumours	Fraxini or Abietis	Osteosarcoma Soft Tissue Sarcoma
Haematologic Neoplasia	Abietis or Fraxini	Leukaemia, Lymphoma
Endocrinous Tumours	Abietis or Amygdali	Carcinoid Thyroid Carcinoma

* The second preparation is used in the case that no reactions according 1- 3 appear.

Metastatic Tumours / Cancer of Unknown Primary

Known primary tumour	Fraxini or the preparation recommended for the primary tumour
Unknown primary tumour	Fraxini

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THERAPY CONSULTATION

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Introduction

ABNOBA GmbH is an independent, medium-sized, research-based pharmaceutical manufacturer based in Niefern-Öschelbronn.

It was founded in 1971 by physicians, biologists, and physicists who were part of the Society for the Promotion of Cancer Therapy (Gesellschaft zur Förderung der Krebstherapie e.V.) in Pforzheim, with the purpose of developing and distributing mistletoe preparations under the brand name abnobaVISCUM®. Long-term basic research into the nature of disease, medicinal plants—particularly mistletoe—and pharmaceutical science, based on the insights of Rudolf Steiner (1861–1925, philosopher and founder of anthroposophic medicine) and Goethe’s scientific methodology, preceded the company’s founding.

The central focus of the company’s work is the oncological patient. ABNOBA GmbH’s shareholders are exclusively non-profit organizations, which means that all company profits are reinvested in cancer research and the development of new medicines.

Today, ABNOBA GmbH is recognized as one of the world’s leading and most innovative companies in the field of herbal medicinal products for oncology.

abnobaVISCUM® preparations have been authorized for use in Germany since 1985/1992, with multiple further authorizations abroad. These recommendations are supported by the Information for Healthcare Professionals and clinical as well as practical experience.

abnobaVISCUM® is applied in adjuvant, supportive, and palliative tumor therapy, as well as in post-treatment cancer care.

abnobaVISCUM sorts and composition

abnobaVISCUM preparations are available from 9 different host trees (sorts), each in the following strengths or potency levels

20 mg, 2 mg, 0.2 mg, 0.02 mg, D6, D10, D20 and D30.

abnobaVISCUM preparations are pharmacy-only medicines (only in Germany).

The following sorts are available:

Name of the medicinal product	English name of the host tree (sort)	
ABNOBAVISCUM®	Abietis	Fir
	Aceris	Maple
	Amygdali	Almond
	Betulae	Birch
	Crataegi	Hawthorn
	Fraxini	Ash
	Mali	Apple
	Pini	Pine
	Quercus	Oak



abnobaVISCUM of the strengths 20 mg to 0.02 mg

are solutions for subcutaneous injection and are available in packaging sizes of 8, 21 and 48 ampoules.

1 ml solution for injection contains

Extract of fresh mistletoe herb (of the respective host tree)
(plant to extract = 1:50) 1 ml/0.1 ml/0.01 ml/0.001 ml

ABNOBAVISCUM®	0.02 mg	(start of therapy)
	0.2 mg	The 20 mg and 2 mg strengths have a yellow-green colour.
	2 mg	
	20 mg	

Extracting agent: *sodium monohydrogen phosphate dihydrate, ascorbic acid, water for injection (2,03 : 0,34 : 97,63)*

abnobaVISCUM in the potency levels D6 to D30

are liquid dilutions for subcutaneous injection. abnobaVISCUM ampoules of potency levels D6, D10, D20 and D30 each contain 1 ml of liquid dilution for injection of Viscum album of the respective host tree ex herba recente col. D6, D10, D20 or D30 and no other ingredients.

For potency levels D10, D20 and D30, the required dose of an infusion solution (physiological saline solution or 5% glucose solution) can be mixed and slowly infused intravenously in special cases. The potency levels D6 to D30 are available in packaging sizes of 8 ampoules of the respective potency level.

Manufacturing and quality assurance of abnobaVISCUM

Harvest

Currently, harvesting is still carried out exclusively by wild collection. Summer and winter mistletoe are used for the production of abnobaVISCUM. Mistletoe is characterized by a number of traits that can be described by both temporal and spatial developmental processes. This, on the one hand, makes the special characteristics of mistletoe understandable in comparison to the plant type, and, on the other hand, provides a ratio for both harvest times. These special characteristics of mistletoe are also evident in its substance spectrum, which is subject to seasonal fluctuations. Harvesting takes place in both summer and winter at predetermined harvest times, which are recognizable by developmental characteristics. The harvested material is divided into portions at the harvest site, frozen in liquid nitrogen, and stored until extraction. This ensures that the harvested material is not only microbiologically stable but also protected from oxidation, thus effectively preventing the degradation of its constituents.

Extraction

The active ingredient in abnobaVISCUM is manufactured in a two-stage process described in the German Homeopathic Pharmacopoeia (HAB). In this process, the mistletoe from the summer and winter harvests is processed separately into pressed juices under exclusion of air using a patented method and extracted with an aqueous ascorbate phosphate buffer solution in such a way that more than 75% of the plant material used becomes dissolved. All the essential ingredients (e.g. mistletoe lectins, viscotoxins) are then contained in the extract in very high yields. The typical yellow-green colour of abnobaVISCUM 20 mg is still recognisable in the 2 mg strength. This colour is due to the fact that the pressed juice contains additional lipid-related components, so-called membrane lipids, in the form of microscopic bubbles (liposomes) as a result of the special

extraction process. These are formed from the cell membranes that occur naturally in the plant cell. The liposomes contain the waterinsoluble green plant dye, chlorophyll, of the mistletoe. Mistletoe liposomes have been shown to have numerous immunological Effects. Natural liposomes contained in the extract contribute to the good tolerability of our medicines.

Further manufacturing steps

Subsequently, the summer and winter pressed juices are mixed using a so-called flow process and diluted with ascorbate phosphate buffer in a defined ratio by spreading the winter pressed juice as a liquid film on the surface of a rotating disc and adding the summer pressed juice in drop form. From the active agent produced in this way, the injection solutions are later manufactured under aseptic conditions (in a clean room area) after sterile filtration and filled into ampoules. Known ingredients such as mistletoe lectins and viscotoxins are heat-labile and therefore cannot be autoclaved, as is usually done with heat-stable drugs.

Quality assurance

The production and quality control of abnobaVISCUM are carried out in accordance with legal regulations, in compliance with strict international standards and the rules of „Good Manufacturing Practice“ (GMP guidelines). These are applied in accordance with the current state of knowledge and technology and are continuously updated. For mistletoe preparations, a number of substances (active ingredients such as mistletoe lectins, viscotoxins, polysaccharides, liposomes, triterpenoids, and many others) are described that contribute to the overall effect. These are not defined individual substances, but rather groups of substances whose individual contribution depends on interactions with the other components (accompanying substances) as well as galenic features (liposomes) of the overall preparation.

For this reason, the pharmaceutical quality of abnobaVISCUM is ensured by process standardization (determination of harvest times, formulation, and manufacturing processes, as well as the application of validated control methods and the definition of specifications). Process controls carried out throughout the entire production process, as well as final inspections, demonstrate that the manufacturing process results in products of consistent quality. Depending on the sort (host tree), the preparations have a different substance composition. For example, the total lectin content of abnobaVISCUM Fraxini is on average 40 times higher than that of abnobaVISCUM Pini of the same extract strength (see figure). Regarding viscotoxins, this difference is only a factor of 7, with the same descending order of the abnobaVISCUM sorts.

Differences between the abnobaVISCUM sorts (host trees)

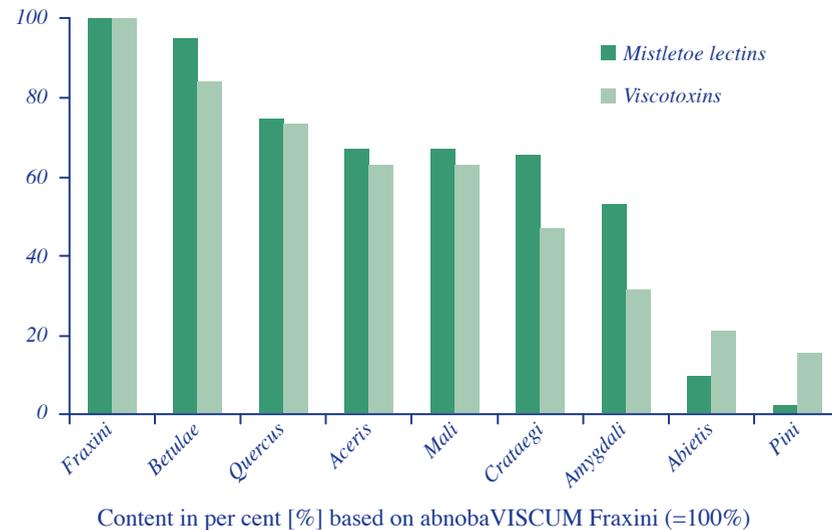


Figure: Differences between the abnobaVISCUM sorts (host trees). Example: mistletoe lectin content. Shown here are the percentage values of the abnobaVISCUM sorts (host trees) in relation to abnobaVISCUM Fraxini (= 100%).

About the ingredients of mistletoe and their effects

Mistletoe is a protein-rich plant. Therefore, numerous substances or groups of substances that are typical of mistletoe are belonging to the proteins. These include mistletoe lectins and viscotoxins. They have been wellinvestigated and have cytotoxic and immune-modulating effects in various ways. *In vitro and in vivo*, mistletoe extracts activate monocytes/macrophages, granulocytes, and their phagocytic capacity, increase the activity of natural killer cells (NK cells) and T cells (especially T helper cells), induce various cytokines (messenger substances), stabilize DNA (deoxyribonucleic acid), reduce chromosomal damage, and improve DNA repair. They inhibit neoangiogenesis, resulting in a reduced blood flow to and from solid tumors. An increased release of the body's own endorphins has also been demonstrated through mistletoe extracts, which influences pain perception and also improves well-being. Other scientifically studied components of mistletoe are oligosaccharides and polysaccharides, which, like the first two mentioned, have desirable immunological properties for the treatment of tumors.

This makes it clear: There is no single active ingredient in mistletoe. The therapeutic principle is not a single substance, but the entire extract.

Mistletoe lectins are sugar-binding proteins that bind specifically to sugar structures on cell surfaces and trigger biochemical reactions there. Mistletoe - and this is rare in the plant kingdom - even contains two different groups of mistletoe lectins: on the one hand the cytotoxic and high molecular mistletoe lectins, on the other hand smaller, only immunologically active, non-cytotoxic so-called chitin-binding mistletoe lectins. The cytotoxic mistletoe lectins bind to the surface of cancer cells. After being absorbed into the cell, they lead to damage and death of these cells by inhibiting protein synthesis and stimulating non-inflammatory cell death through apoptosis.

Viscotoxins are small surface-active, strongly basic proteins that can interact with numerous substances. They react quickly, more quickly than mistletoe lectins, and unlike mistletoe lectins they do not lead to cell death without inflammation. The cell fluid leaks into the surrounding tissue, causing an inflammatory reaction (necrosis).

Evidence of the cytotoxicity of mistletoe extracts and preparations is available for a large number of tumor cells both in vitro and in vivo. It is comparable to the cytotoxic properties of conventional chemotherapeutic agents in the respective cell culture systems.



Special features of abnobaVISCUM

abnobaVISCUM differs from other mistletoe preparations through:

- **Harvest**
Harvest times are based on the plant's development throughout the year, not on cosmological considerations.
- **Careful exclusion of microbial degradation**
Standardized production prevents microbial spoilage or the degradation of ingredients right from the harvest. Fermentation also does not occur during production.
- **No oxidative changes to the active ingredient**
abnobaVISCUM is manufactured under protective gas from the storage of the harvested material to the filling in ampoules, thus eliminating oxidative changes, which can be recognized by the brown color of similar preparations.
- **High mistletoe lectin and viscotoxin levels**
Due to the patented production of the pressed juice, more than 75% of the plant material used dissolves. This results in reproducibly high concentrations of mistletoe lectins and viscotoxins in the extract. It is worth emphasizing that both groups of ingredients are equally well extracted and both substance groups are present in high concentrations in abnobaVISCUM.
- **Liposomal processing**
Natural liposomes contained in the extract contribute to the good tolerance of our medicinal products.

Recommendations for the use of abnobaVISCUM

AbnobaVISCUM is, in addition to other approvals abroad, approved in Germany for the following indications.

Indications

abnobaVISCUM is used in adults for:

- Prevention of relapses after tumor surgery
- Treatment of benign tumors
- Treatment of malignant tumors, even with accompanying disorders of the blood-forming organs
- Treatment of defined precancerous lesions

abnobaVISCUM is used as a supportive treatment for chemotherapy and radiotherapy, as well as before or after surgery to improve quality of life or reduce the side effects of standard therapies. After completion of standard therapies, abnobaVISCUM is used for immunomodulation to strengthen the entire organism and prevent relapses.

Mistletoe therapy can reduce pain that occurs in advanced tumor stages through its stimulating effect on endorphin release.

The loss of appetite and disturbed sleep patterns that often occur in connection with cancer can be remedied or alleviated. For specific information on supportive therapy, please refer to the chapter „abnobaVISCUM in combination with other therapies“ on page 32.

Contraindications

- known hypersensitivity to mistletoe preparations
- acute inflammatory or highly febrile diseases: treatment should be interrupted until the signs of inflammation subside

- chronic granulomatous diseases and florid autoimmune diseases and those treated with immunosuppressive therapy
- hyperthyroidism with tachycardia

Side effects

abnobaVISCUM is well tolerated when used as directed. The most common side effects are local reactions, such as localized redness at the injection site, which may also be accompanied by hardening, swelling, itching, warmth, or pain. Serious adverse events attributable to mistletoe therapy are rare.

The following symptoms occur almost regularly with the correct individual dosage:

Skin, skin appendages: Locally limited inflammatory reaction up to 5 cm in diameter around the site of the subcutaneous injection (local reaction), usually occurs 8 to 12, rarely 24 hours after the injection and can last for several days

General: Slight increase in body temperature, usually occurs within 12 hours of the injection

Blood and lymphatic system: Temporary mild swelling of regional lymph nodes

The symptoms described here are harmless. They indicate the patient's responsiveness. A slight temperature increase (up to 38°C) caused by abnobaVISCUM should not be suppressed with antipyretics.

However, if the following side effects occur, the strength and timing of the next injection have to be adjusted accordingly:

Skin, skin appendages:	larger local inflammatory reactions over 5 cm in diameter, nodular hardening of the subcutaneous tissue at the injection site
General:	Fever over 38 °C, fatigue, chills, general malaise, headache, temporary dizziness, activation of pre-existing inflammation
Blood and lymphatic system:	Larger swelling of regional lymph nodes, inflammatory irritation of superficial veins in the injection area

The general symptoms described here are not a sign of intolerance, but rather indicate an effective dosage. However, if these symptoms have not subsided within the day following the injection or exceed a tolerable level, the dose should be reduced to the next lower strength. The next injection should then only be given after these symptoms have subsided. If fever persists for more than three days, it is generally not considered a side effect of the mistletoe injection; other causes should be sought.

There are only a few situations in which the following allergic or allergoid reactions may occur:

Skin, skin appendages:	local or generalized itching, urticaria, exanthema, erythema exsudativum multiforme, Quinke oedema
General:	whole body itching, chills
Cardiovascular system:	shock
Respiratory system:	dyspnea, bronchospasm

If these symptoms occur, abnobaVISCUM must be discontinued immediately. Emergency medical measures should be administered in accordance with current guidelines. Adequate emergency equipment must be available.

Reports have been made of:

- the occurrence of chronic granulomatous inflammation (sarcoidosis, erythema nodosum) and autoimmune diseases (dermatomyositis) during mistletoe therapy
- and symptoms of increased intracranial pressure in brain tumors/metastases during mistletoe therapy

Special warnings and precautions for use

If the dose is increased too quickly, for example, if a strength is skipped, allergoid reactions may occur, requiring emergency medical intervention (see above). These symptoms are dose-dependent and not caused by an allergy. Therefore, treatment can be continued at a reduced dose after symptoms have subsided.

After any break of more than 4 weeks, always restart with the 0.02 mg strength to determine the individual dose.

In cases of primary brain and spinal cord tumors or intracranial metastases with a risk of increased intracranial pressure, the preparations should only be administered after strict indication and under close clinical monitoring.

Before use, the ampoule should be briefly warmed in the hand.

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization is of great importance. It enables continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reaction to the Federal Institute for Drugs and Medical Devices (BfArM).

Federal Institute for Drugs and Medical Devices (BfArM)

Dept. of Pharmacovigilance,
Kurt-Georg-Kiesinger Allee 3,
D-53175 Bonn,
Website: www.bfarm.de



Posology in cases of impaired renal function

There is insufficient data for concrete dosage recommendations in cases of impaired renal function. General experience to date has not indicated a need for dose adjustment.

Interactions with other medicinal products and other interactions

The induction of various CYP450 isoenzymes was tested with abnobaVISCUM Fraxini 20 mg, Abietis 20 mg and Pini 20 mg. Based on these studies, no interactions with other medicinal products are to be expected. There are no investigations available on interactions with other immune modulating substances (e.g., thymus extracts). When administering relevant preparations at close intervals, careful dosage and monitoring of appropriate immune parameters is recommended.

Fertility, pregnancy and lactation

There are no clinical data available on pregnant women exposed to abnobaVISCUM. Preclinical embryotoxicity studies conducted in rats with abnobaVISCUM Fraxini 20 mg do not indicate any special risks to humans. There are no investigational studies on animals available

regarding the effects on delivery and postnatal development, in particular on hematopoiesis and the immune system of the fetus/infant. The potential risk to humans in these areas is unknown. Caution is advised when used during pregnancy and lactation.

Effects on ability to drive and use machines

No studies have been conducted on the effects on the ability to drive or use machines. It is therefore not known whether abnobaVISCUM affects the ability to drive or use machines. However, if symptoms such as fever occur that are related to the use of abnobaVISCUM, the patient must not actively participate in road traffic or operate machinery until these symptoms have subsided.

Selection of the sort (host tree)

The abnobaVISCUM sorts differ in the trees on which the mistletoe grows, the so-called host trees. The choice of the sort depends on the location and type of tumor. Recommendations can be found in the table of the front cover fold-out.

Dosage

Treatment with abnobaVISCUM is initiated gradually. Dosage increases and frequency of administration are adjusted to the patient's response. The dose is increased until the optimal dose (individual dose) for the patient is reached.

Initiation phase

Dosage and frequency of administration (for all abnobaVISCUM preparations):

Unless otherwise stated, the dosage is always 1 ml of the injection solution of the specified strength or potency. Treatment should be initiated with the 0.02 mg strength three times a week. Then the dose is gradually increased until the optimum dose is reached.

Maintenance phase

Unless otherwise prescribed:

The individual dosage may already be achieved with the 0.02 mg strength. Otherwise, the dose is gradually increased to the 0.2 mg, 2 mg, and 20mg strengths, each with 2-3 injections per week.

Start of therapy

It is recommended to start treatment with 1 ml (one ampoule) of 0.02mg 3 times a week.

The basic procedure for increasing the dose, supported by many years of clinical experience, can be found in the treatment schedule (front cover, inside back flap). The reactions described below under „Individual Dosage“ are regularly to be expected.

If no or only a slight reaction is observed after 8 injections of the 0.02 mg strength, the dosage is increased to 0.2 mg, also with 3 injections per week.

If no or only a slight reaction is observed after 8 injections, the dosage is increased to 2 mg, also with 3 injections per week.

If one of the reactions listed under a) to d) below occurs, this dosage is maintained until no further reactions are observed.

Potency levels D6 to D30 are to be used according to the individual indication (see later in a separate chapter on p. 30).

Individual dose

The individual dose is the one at which at least one of the following reactions occurs:

a) Local inflammatory reaction (local reaction)

At the injection site, a local inflammatory reaction typically occurs after 8 to 12 hours, rarely only after 24 hours. This localized inflammatory skin reaction should have a maximum diameter of 5 cm. It subsides over the next two to three days and becomes progressively weaker over the course of treatment.

b) Temperature reaction

Three types of temperature reactions can be observed:

Immediate Reaction: A rise in temperature occurs within the first 12 hours after the injection. This temperature reaction (immediate reaction) usually disappears after several weeks of continuous therapy at a constant dosage.

Rhythmic Reaction: Restoration of the physiological morning/evening temperature difference of at least 0.5°C is observed.

Delayed Reaction: Over the course of the treatment, the average temperature level increases. In the case of tumor fever, normalization and rhythmicization of core temperature are targeted using low concentrations.

Note: For the sake of comparability, temperature measurements should, if possible, be taken in the morning and afternoon/evening using the same method and at the same times.

c) Immunological reaction

Stimulation of the specific and non-specific immune system. A positive immune system reaction can be demonstrated by changes in leukocytes, especially through maturation and activation of lymphocytes and by an increase in eosinophils. An improvement in cellular immune status can also be observed in the determination of lymphocyte subpopulations as well as in the number and activation of NK cells. However, these observable pharmacodynamic effects also depend on the initial dosage and change over the course of therapy.

After 3 to 9 weeks, antibodies against mistletoe proteins (mistletoe lectins, viscotoxins), usually of the IgG type, usually appear.

d) *Change in well-being*

After the temperature reaction subsides, a regular improvement in general well-being and mental state, an increase in initiative and performance, and, where appropriate, pain relief as well as improved appetite and weight gain occur. A reduction in the dosage of any necessary analgesics can be considered.

If excessive reactions occur when switching from one strength to the next higher, only half an ampoule should be injected during the next dose of that strength.

Opened ampoules must not be reused for subsequent injections.

If excessive reactions occur even with the 0.02 mg strength, you should switch to the D6 or D10 potency. If excessive reactions occur here as well, only one-third of the D6 ampoule should be used, or you should switch to D10 or to a different type of abnobaVISCUM.

The D6 potency is a liquid dilution of the 0.02 mg strength in a ratio of 1:10 with 0.9% saline solution.

abnobaVISCUM preparations of the same strength but different sorts (different host trees) differ considerably in their quantitative composition. For example, abnobaVISCUM Fraxini contains approximately 40 times more mistletoe lectins than abnobaVISCUM Pini (see the chapter „Quality assurance“ p. 14 illustration). When switching to a different sort, a different patient reaction to the injection must be expected. Therefore, a lower strength/dose should be injected initially when switching.

If the patient's response changes during treatment (e.g., due to concurrent radiotherapy or chemotherapy), the individual dose should also be readjusted.

To avoid habituation,

- a rhythmic application is recommended, alternating between lower concentrations or doses in the form of ascending and possibly descending doses
- or by re-rhythmicizing the injection intervals.

The dosage should be reviewed every 3–6 months based on patient response and tumor behavior.

**OVERDOSAGE / Overreaction:
symptoms, emergency measures, antidotes**

Increasing the dose by more than one strength must be avoided absolutely. The procedure for determining the individual dose must be followed. A dose increase that is too rapid (e.g., skipping the next higher dose to the next) may result in allergic reactions that require emergency medical intervention (see below). Since the allergic reaction is dose-dependent, treatment can be continued at a reduced dose after symptoms have subsided.

If anaphylactic reactions occur: signs of an incipient anaphylactic reaction include itching or burning on the palms of the hands or soles of the feet, the tongue, or the palate, as well as itching, erythema, and urticaria on the skin and mucous membranes. Further, nausea, cramps, vomiting, rhinorrhea, hoarseness, dyspnea, tachycardia, and a drop in blood pressure may occur, leading to shock and cardiac arrest.

Emergency treatment for anaphylactic reactions is carried out according to current guidelines. Adequate emergency equipment must be available.

Duration of treatment / continuous therapy

After determining the individual dose (see page 25), therapy is continued with 2-3 weekly subcutaneous injections of this dosage. There is, in principle, no limit to the duration of treatment. It is determined by the physician and depends on the respective risk of tumor recurrence and the individual findings and condition of the patient. It should last several years, with breaks of increasing length generally being taken.

The following procedure is commonly used and should be considered a suggestion:

- If the patient feels well, the dose can be reduced to two ampoules per week after two years.
- While maintaining this injection frequency, breaks of 1–3 weeks up to a total of 3 months can be taken in the third year. In the fourth year of treatment, two breaks of up to 3 months each can be taken. From the fifth year of treatment, the treatment duration at the last dose used can be limited to 3 months per year. After 5–7 years, if the patient feels well, the therapy can be discontinued.

The therapy can also be continued beyond a period of 7 years, e.g., as part of recurrence prevention.

Therapy breaks

After breaks lasting longer than 4 weeks, treatment is always restarted with the 0.02 mg strength, as described in the section „Individual dose“ (see page 25).

**Method of administration and injection sites
Subcutaneous injection**

This subcutaneous (under the skin) method of administration is easy to learn and can be easily administered by the patient himself or a family member without risk, preferably in an easily accessible area of the body. Injections under the abdominal skin are recommended as the injection site. The injection is administered subcutaneously, if possible alternating, e.g., once in the right side of the abdomen and the next injection in the left side of the abdomen. Injections into inflamed skin areas (e.g., local reaction/lymph nodes), radiation fields, or near surgical scars should be avoided. In these cases, injections into the thigh or upper arm are recommended.

Rest is recommended after the injection.

Intravenous infusion

In special cases, intravenous infusion of abnobaVISCUM in potency levels D10 – D30 can be administered. Dosage and frequency depend on the patient's physical condition and are determined individually. abnobaVISCUM is administered in the respective dose in 250 ml of sterile physiological saline solution as an intravenous infusion. The infusion should last at least 90 minutes.

This only applies to D10 to D30 preparations. For other strengths, a so-called „off-label use,“ an infusion duration of at least 120 to 150 minutes must be observed.

If symptoms of an allergic reaction occur during the infusion, the infusion must be discontinued immediately. If the symptoms do not subside, emergency medical measures (see page 28) must be taken.

For the use of D-potency levels (D6, D10, D20 and D30)

The D potencies are also administered subcutaneously, independently of the above dosage schedule, individually or alternately – also with the mg strengths (see „Individual Dosage“ on page 25) – 1-2 times per week, especially for weakened patients, for strengthening purposes as part of a homeopathic therapy concept. For host tree selection, please refer to our host tree recommendations (see table at the beginning of this brochure). Coniferous sorts in high potencies are particularly suitable for weakened patients. Other dosages, such as daily or every other day, are also possible and are based on the patient's condition.

Other types of use („off label use“)

Off-label uses are all uses outside the scope of the approved drug authorization, i.e., uses other than the approved subcutaneous route (see above), such as intravenous, intravesical, intrapleural, or intratumoral administration of abnobaVISCUM. This also includes a dosage regimen other than the approved one, for example, starting immediately with a high dose.

For the following described uses of abnobaVISCUM, we recommend seeking advice from our medical-scientific service.

- Intravenous infusion of strengths D6 and 0.02 mg to 20 mg
- Instillation e.g., malignant pleural effusion, bladder carcinoma, ascites
- Treatment with an increased initial dose e.g., in patients in good general health who have not yet been pretreated with mistletoe preparations
- Intratumoral injection

Off-label uses of abnobaVISCUM beyond its approved authorization are generally also considered safe when administered by experienced physicians (see also „Current Study Status“). They are the sole responsibility of the physician and require the patient's written consent.

OTHER THERAPY CONSULTATION

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abnobaVISCUM in combination with other therapies

During radiation and chemotherapy and after surgery, the patient's response to the abnobaVISCUM injections may change. A re-evaluation of the individual dose, starting at 0.02 mg, may be necessary in rare cases (see page 25).

- **Surgery**
Surgical procedures and anesthetics can have an immunosuppressive effect. Therefore, it is recommended that abnobaVISCUM is administered for immune modulation preoperatively if possible, even if only a short period of time is available before surgery. Start with the strength 0.02 mg 3 times per week. After surgery, mistletoe therapy should be discontinued until wound healing is complete.
- **Chemotherapy**
Treatment with abnobaVISCUM can reduce the side effects of chemotherapy. Negative interactions between the use of abnobaVISCUM and concurrent chemotherapy are not known. An improved quality of life has been clinically proven with chemotherapy and concurrent mistletoe therapy. Generally, the immunosuppressive effect of chemotherapy is too strong to achieve a simultaneous stimulation of the immune system. The focus is therefore on improving the tolerability of chemotherapy and the quality of life of the patient. The dosage is based on the general guidelines described on page 24. If mistletoe therapy is only started during chemotherapy, a cautious, gradual dosage should be used.

- **Radiation therapy**
During radiation treatment, treatment with abnobaVISCUM can be administered, but the radiation field must be strictly avoided as an injection site. Under certain circumstances, a dose reduction may be necessary due to a change in the patient's reactivity (especially a tendency to inflammatory reactions).
- **Hormone therapy**
During hormone therapy, treatment with abnobaVISCUM can be administered, but attention must be paid to changes in the patient's reactivity.
- **Combination with modern immunotherapeutics**
abnobaVISCUM can be combined with modern immunotherapeutics. Their effects are not negatively influenced, enhanced, or extended. A multicenter observational study showed that additional mistletoe therapy with abnobaVISCUM significantly reduced treatment discontinuations by more than half in targeted therapy (monoclonal antibodies, immunotherapeutics, tyrosine kinase inhibitors).

Current study status

Clinical studies with mistletoe preparations consistently report that mistletoe therapy in cancer patients primarily leads to a better quality of life and improved tolerance to chemotherapy.

General well-being improves, as do energy and vitality, emotional well-being, concentration, sleep, and appetite. Patients also suffer less from exhaustion, nausea, vomiting, pain, and shortness of breath, and they are less burdened by sadness, anxiety, depression, irritability, and worry. Likewise, improved self-regulation in stressful situations, i.e., for example the autonomy and self-activity of the individual, with which they can achieve inner balance and a sense of competence and security, is observed.

There is strong evidence of an extension of survival time in cancer patients with subcutaneous mistletoe therapy. The question of whether mistletoe preparations have a direct effect on tumors has so far remained unanswered in the above-mentioned controlled clinical trials. Only a few smaller studies address this issue: a Phase I/II study on dose-finding, safety, and efficacy in bladder cancer of abnobaVISCUM, further observational studies or case series and a whole series of very well-documented case reports showing tumor regression under mistletoe therapy. In these cases, mistletoe preparations were usually administered in high doses and close to the tumor. Overall, however, such regressions under mistletoe therapy are rarely observed.

Furthermore, clinical trials, systematic reviews, and health services research studies have examined the safety of mistletoe therapy, with the result that mistletoe therapy is safe to use. It is characterized by good tolerability with only mild side effects; no serious or life-threatening events have been observed.

Studies on drug interactions with other medications have also been conducted within the scope of health services research. Mistletoe preparations do not negatively influence other cancer therapies. This has been demonstrated for antihormonal substances used primarily for breast cancer (e.g., tamoxifen, anastrozole) and some antibody therapies (e.g., trastuzumab, pertuzumab). No adverse effects have been observed with so-called immune checkpoint inhibitors (e.g., ipilimumab and nivolumab). The side effect profile of modern immunotherapeutics has not been amplified or expanded. An initial positive effect of mistletoe in this context was shown by a health services research study in which additional mistletoe therapy with abnobaVISCUM was able to significantly reduce treatment discontinuations in the context of targeted therapy, including immune checkpoint inhibitors, by more than half.

Conclusion: Based on the totality of clinical studies to date and the approved indications, the following picture emerges for mistletoe in tumor therapy:

Patients benefit from mistletoe therapy in all phases of cancer. The effects of mistletoe in tumor therapy are:

- Improvement in quality of life: including fatigue, sleep (quality), appetite, strengthening, reduced susceptibility to infections, and restoration of work capacity.
- Tumor remissions (only in single cases after high doses).
- Strong evidence of prolonged survival: Patients live longer with a good quality of life, and disease progression is slowed.
- Reduction in the side effects of conventional oncological therapies.

Numerous cancers at all stages can be treated with mistletoe preparations. Mistletoe therapy can be administered before, during, or after conventional treatment.

For further information on the current study status, we recommend the additional information sources listed at the end of these recommendations.

Pharmacokinetic studies with abnobaVISCUM

Mistletoe lectins from abnobaVISCUM Fraxini 20 mg are detectable in serum after a single subcutaneous injection. This was shown by pharmacokinetic studies in healthy male volunteers aged 18–42 years. The detectability of native mistletoe lectins in serum is considerably longer than that of recombinant mistletoe lectin. The maximum concentration was reached 1–2 hours after injection. In some volunteers, mistletoe lectins were still detectable in the serum at the final examination 2 weeks after the injection. The injection caused temporary fever and flu-like symptoms in all subjects. No serious adverse events occurred. All symptoms and local reactions at the injection site disappeared completely.

Preclinical safety data

The acute toxicity of abnobaVISCUM Fraxini 20 mg and abnobaVISCUM Pini 20 mg was investigated in male and female rats and mice following subcutaneous and intravenous application.

In a 28-Day dose-range-finding study on subacute toxicity 3 doses were tested in male and female rats: 0.2, 0.66 and 2 ml per kg rat body weight of abnobaVISCUM Fraxini 20 mg were administered daily by subcutaneous injection from day 1 to 5 and changed to thrice weekly from day 6 onwards. The derived maximum tolerated dose (MTD) is 2 ml/kg body weight/day when administered thrice weekly.

In a 90-Day subchronic toxicity study a NOAEL of 2 ml/kg body weight/day was determined by administration of 3 different doses (0.2, 0.66 and 2 ml abnobaVISCUM Fraxini 20 mg/kg/day injected subcutaneously thrice weekly) in male and female rats. Investigations on chronic toxicity were not conducted.

Animal safety pharmacology studies (mouse, rat, dog) with subcutaneously injected abnobaVISCUM Fraxini 20 mg revealed no special safety risks for humans

Animal experiments on immunotoxicity in the mouse, which were conducted representatively with the abnobaVISCUM product containing the most lectins (abnobaVISCUM Fraxini 20 mg), showed no immunotoxicologically relevant impact on general and specific immune parameters or on the humoral and cellular immune response at doses up to four times greater than the daily maximum therapeutic dose. In further animal experiments, there was evidence of a weakening of the resistance to mouse melanoma cells at doses four times greater than the daily maximum dose of the preparation abnobaVISCUM Fraxini 20 mg.

Embryotoxicity studies with 3 different doses (subcutaneous injections of 0.25, 0.75 and 2.25 ml of abnobaVISCUM Fraxini 20 mg per kg rat body weight/day over 12 consecutive days from day 6 to day 17 of pregnancy (organogenesis) were performed in pregnant rats. The systemic no-observed-effect level (NOEL) was 0.25 ml/kg rat body weight/day abnobaVISCUM Fraxini 20 mg without signs of embryotoxicity in the rat dams. Based on these rat embryotoxicity studies the preclinical data do not indicate a special risk for humans.

In 2 in-vitro studies with abnobaVISCUM Fraxini 20 mg, the Ames test (*Salmonella typhimurium*) and the chromosome aberration test (human

lymphocytes) as well as an in vivo micronucleus test (murine bone marrow cells) gave no indication of mutagenicity or cytogenetic damage (clastogenicity/chromosome breaks, small nuclei) as defined by the tests carried out.

Pharmaceutical particulars

Incompatibilities:	Not known. As a precaution, it is recommended that abnobaVISCUM is not to be drawn up in a syringe with other medicinal products.
Shelf life:	abnobaVISCUM of the strengths 20 mg to 0.02 mg has a shelf life of 3 years. abnobaVISCUM of the strengths D6 to D30 has a shelf life of 5 years.
Special precautions for storage:	Strengths 20 mg to 0.02 mg: Store in a refrigerator (2 - 8°C). Do not freeze. Strengths D6 to D30: Do not store above 25°C. Do not freeze. Storage in a refrigerator is recommended.
Transport:	For transport, for example from the pharmacy to the patient, continuous cooling is not required. Extreme temperatures such as frost or heat (above 25°C) should be avoided.

Nature and contents of the container:

abnobaVISCUM is supplied in break-open ampoules containing 1 ml solution for injection. The 20 mg and 2 mg strengths are yellow-green in color. All other strengths or potencies are colorless.

Instructions for handling:

Since abnobaVISCUM is manufactured under strict oxidation protection, it should be injected immediately after opening the ampoules.

Opened ampoules must not be used for subsequent injections.

Likewise, ampoules with brown-colored contents must not be used, as this brown color indicates the ingress of atmospheric oxygen and thus damage to the ampoule.

Disposal of the ampoules:

There are no special requirements for the disposal of the ampoules. Both full, unused and empty ampoules do not belong in the glass waste, but in the household waste as they are made of special glass.

Prescription status / Pharmacy requirement:

Pharmacy only

Books

Selected additional information sources partly only in German

Bopp A.: Mistletoe - a medicinal plant in cancer therapy. Rüffer & Rub, Zurich, 2006

Büssing A.: Mistletoe - The Genus *Viscum*, Harwood Academic Publishers, Amsterdam, 2000.

Society of Anthroposophic Physicians in Germany: Vademecum Anthroposophic Medicines. 4th edition, volume 2, 2017.
The 5th edition has already been announced (details at www.merkurstab.de)

Kienle G.S., Kiene H., Albonico H.-U.: Anthroposophic medicine in clinical research, efficacy, benefits, cost-effectiveness, safety
Schattauer Verlag, Stuttgart, New York, 2006

Kienle G.S., Kiene H.: Mistletoe in oncology - facts and conceptual foundations. Schattauer Verlag, Stuttgart, New York, 2003.

Scheer R., Alban S., Becker H., Beer A.-M., Blaschek W., Klein R., Kreis W., Leneweit, G., Matthes H., Spahn G., Stange R. (Eds.): Mistletoe in tumor therapy - 5, current research and clinical application, 607 pages,
KVC Verlag, Essen 2020, ISBN 978-3- 96562-030-8 and further proceedings of the mistletoe symposia
(see symposium homepage www.mistelsymposium.de)

Wilkens J.: Mistletoe therapy, differentiated application of mistletoe according to host trees, Sonntag-Verlag Stuttgart, 2006

Wilkens J.: Mistletoe - powerful cancer healers from nature, AT-Verlag Aarau, Munich, 2016

Websites

www.abnoba.de

www.mistel-therapie.de - website in German, English, Spanish, and Portuguese of the School of Spiritual Science - Medical Section at the Goetheanum, Dornach, Switzerland

www.biokrebs.de/images/download/Therapie_Infos/Mistel.pdf
Information on mistletoe therapy on the homepage of the Society for Biological Cancer Defense, Heidelberg

www.krebsinformationsdienst.de/behandlung/unkonv-methoden/mistel.php
Information on mistletoe therapy from the Cancer Information Service of the German Cancer Research Centre, Heidelberg

For patients

we recommend our brochure on mistletoe therapy, which is available in German and English. Digital additionally in Dutch, Spanish, and Turkish.



**For further literature and information on special forms of therapy,
please contact:**

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