RECOMMENDATIONS FOR USE

ABNOBA GmbH
Hohenzollernstraße 16
75177 Pforzheim | Germany

Phone +49 (0) 72 31 - 31 50 50
Fax +49 (0) 72 31 - 35 87 14
eMail: info@abnoba.de
www.abnoba.de

ABNOBA VISCUM®

Information for Healthcare Professionals

OVERVIEW

Start of treatment and how to reach optimal dosage (detailed description, page 22)

ABNOBAVISCUM®

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)

Weeks 1 - 3

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

1 Local inflammatory reaction at the injection site up to Ø = 5 cm.

2 Temporary 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.

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

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 exhaustion, mild shivering, generally feeling unwell, headaches and short dizzy spells that can arise on an injection day are signs of correct dosage, as long as these reactions subside within 12 hours.

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

Weeks 3 - 6

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 opposite).

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.

Week 6 onwards

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

Or: In cases of poor general condition or if the patient has a strong/severe reaction, 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.

Week 6 onwards

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 Ø and smaller than 10 cm Ø:
Reduce injection amount to 0.5 ml (½ ampoule) for the next 3 injections.
the local inflammatory reaction is larger than 10 cm Ø:
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 persist:
Continue treatment with abnobaVISCUM potency D6 of the same host tree.

* See page 26 for further important information on overdosage.

Long-term therapy

Once the individual optimal dosage has been reached, from Week 6 onwards the following process is often followed:

Injections s.c. are maintained at 3 x per week for up to 2 years. Then 2 x per week for 1 further year.

After 3 years, treatment-free intervals of 3 months can be introduced.

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

Choosing the type 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 Cervial Carcinoma
Urogenital Tumours	male: **Crataegi** or Quercus female: **Mali** or Pini	Bladder Carcinoma Testicular Carcinoma Renal Cell Carcinoma Carcinoma of the Prostata
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
Paediatric Tumours Solid and Haematological Tumours	**Fraxini** or Abietis	Leukaemia Lymphoma Neuroblastoma

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

Tumours with metastases

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

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TREATMENT ADVICE

Our specialists can be consulted regarding treatment with abnobaVISCUM Please contact us at:

Phone +49 (0)7231 - 31 50 50 Fax: +49 (0)7231 - 35 87 14
E-mail: info@abnoba.de

Introduction

abnobaVISCUM mistletoe preparations were first used in 1971. The experience gained in clinical and private practice since provides the basis of the following recommendations for administering the treatment.
abnobaVISCUM is used in supportive, adjuvant and palliative tumour therapy programs as well as in post-operative treatment of tumour disease. As it is an anthroposophical mistletoe preparation, the costs are refundable within the context of a cancer treatment plan (in Germany).

Types of abnobaVISCUM and composition

abnobaVISCUM preparations are produced from nine different host trees (types). Each type of preparation is available in the following strengths: 20 mg, 2 mg, 0.2 mg, 0.02 mg, D6, D10, D20 and D30.
abnobaVISCUM preparations are ethical drugs or pharmacy-only medicines (only in Germany).

The following types of preparations are available:

Name of the medicinal product		English name of host tree (type)
ABNOBAVISCUM®	Abietis	fir
	Aceris	maple
	Amygdali	almond
	Betulae	birch
	Crataegi	hawthorn
	Fraxini	ash
	Mali	apple
	Pini	pine
	Quercus	oak

abnobaVISCUM: 0.02 mg to 20 mg strengths

Solution for subcutaneous injection. Each concentration is available in packages of 8, 21 and 48 ampoules.

1 ml of injection solution contains:		
	Pressed juice from the mistletoe plant of the particular host tree, produced from … mg mistletoe	
ABNOBAVISCUM®	0.02 mg 0.2 mg 2 mg 20 mg	**(Start of treatment)** Note: The 20 mg and 2 mg strength injection solutions have a yellow-green colour.

Excipients*: *Disodium hydrogen phosphate, sodium dihydrogenphosphate, ascorbic acid, water for injections*

abnobaVISCUM: D6 to D30 strengths

Solution for subcutaneous injection, intravenous infusion or instillation into body cavities. Each strength is available in packages of 8 and 48 ampoules.

Strengths D6 to D30:

	Strength	An ampoule of 1 ml solution for injection contains:
ABNOBAVISCUM®	D6	Viscum album *of a specific host tree* ex herba recente col. D6: 1 ml
	D10	Viscum album *of a specific host tree* ex herba recente col. D10: 1 ml
	D20	Viscum album *of a specific host tree* ex herba recente col D20: 1 ml
	D30	Viscum album *of a specific host tree* ex herba recente col. D30: 1 ml

Excipients*: *None*

* Note for patients with coeliac disease:
abnobaVISCUM does not contain any gluten.

Old and new designations

In 2006 the designations of abnobaVISCUM mistletoe preparations were simplified by omitting the dilution step 2 to 30 (see following table).

New designation			Old designation	
ABNOBAVISCUM®	(type e.g. Mali)	20 mg	-2	20 mg
	(type e.g. Mali)	2 mg	-3	2 mg
	(type e.g. Mali)	0.2 mg	-4	0.2 mg
	(type e.g. Mali)	0.02 mg	-5	0.02 mg
	(type e.g. Mali)	D6	-6	D6
	(type e.g. Mali)	D10	-10	D10
	(type e.g. Mali)	D20	-20	D20
	(type e.g. Mali)	D30	-30	D30

This amendment relates to the designations of the preparations and not to any alterations in the actual medicine. In order to prevent error and confusion it became necessary to clarify the differences between stronger and weaker concentrations.

Production and quality control of abnobaVISCUM

Harvest

abnobaVISCUM is produced using summer and winter harvests. The mistletoe plant is distinguished by a series of characteristics which can be described in terms of time-related and space-related biological development processes. In this way the unique features of the mistletoe can be understood in relation to other plants within its species and a rationale for harvesting the mistletoe becomes apparent. These specific features can also be observed in the mistletoe's spectrum of substances which is subject to seasonal variations. For this reason, mistletoe is harvested in summer and winter, at times that are predefined in accordance with the particular characteristics of biological development. Plant materials are apportioned and deep-frozen in fluid nitrogen at the harvest site and then stored until the extraction process. This provides for microbiological stability and prevents oxidation.

Extraction

The active ingredient in abnobaVISCUM is produced by means of the two-step procedure described in the Deutsche Homöopathische Arzneibuch (HAB) [German Homeopathic Pharmacopoeia]. The summer and winter harvests are treated separately according to a patented pressing procedure under protective atmosphere. The extraction is carried out using a ascorbate phosphate buffer solution so that 75% of plant materials are retained in the solution. This ensures that the mistletoe extract contains a high yield of all main ingredients (e.g. mistletoe lectins, viscotoxins). abnobaVISCUM 20 mg and 2 mg strengths have typically a yellow-green colour. This is due to the special extraction that retains additional fat-related substances, the so-called 'membrane lipids' in the extract, in the form of tiny bubbles called liposomes. These liposomes are formed from the cell membranes occurring naturally in plants and contain green mistletoe plant pigment. Numerous immunological effects have been reported for mistletoe liposomes, and they probably explain why abnobaVISCUM is well-tolerated.

Further production steps

The summer and winter extracts are mixed together in a so-called "flow process" and then diluted with the ascorbate-phosphate buffer according to a predefined formula. A liquid film of winter extract is spread over the surface of a rotating disk while the summer extract is added dropwise. The resulting active ingredient is used later on to produce the injection solutions which are finally filled into glass ampules by means of sterile filtration under aseptic conditions.

Quality assurance

Manufacture of abnobaVISCUM and quality control procedures are carried out according to legal regulations and in strict adherence to international standards and rules of "good manufacturing practice", i.e. the GMP guidelines. These regulations are applied and continually updated according to the most current knowledge and technology. A series of substances have been detected in mistletoe preparations that contribute to the overall effect of the remedies (active substances such as mistletoe lectins, viscotoxins, polysaccharides, liposomes, triterpenoids, amongst many others). These are not defined individual substances but rather substance groups. The contribution of each substance group to the overall medicinal preparation depends on its interactions with other constituents, i.e. secondary substances, as well as on galenic features (liposomes). Therefore the pharmaceutical quality of abnobaVISCUM is ensured by means of process standardization, i.e. fixing of harvest times, formulas, production processes and specifications, and employment of validated control methods.

Controls carried out during production and at the end of the entire manufacturing process show that the mistletoe preparations are of consistent quality.
The substance composition of each type (i.e. host tree) of mistletoe preparation is different. For example, the total lectin content of abnobaVISCUM Fraxini is 50 times higher on average than the same extraction strength of abnobaVISCUM Pini. See Figure 1 and 2.

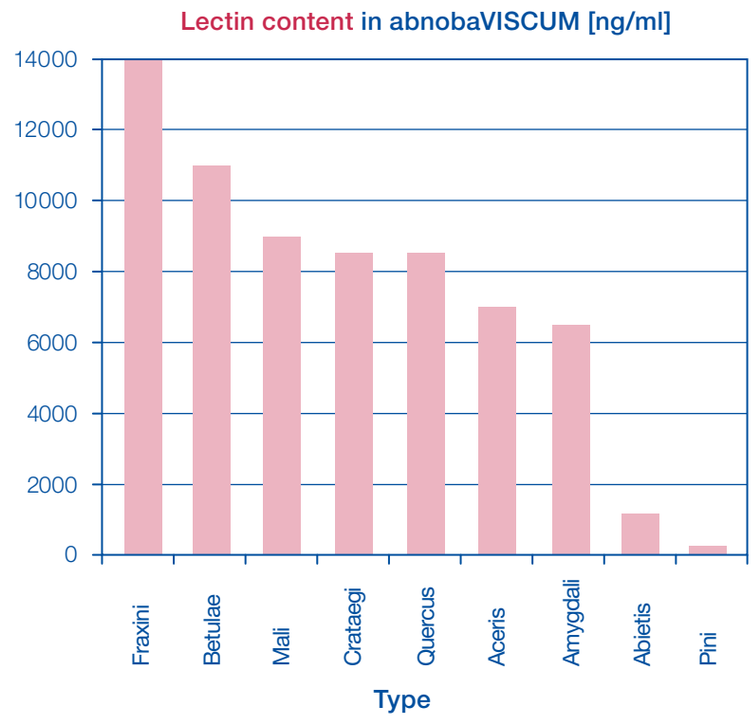

Figure 1: *Average total lectin content of abnobaVISCUM preparations, strength 20mg, according to host tree (type).*

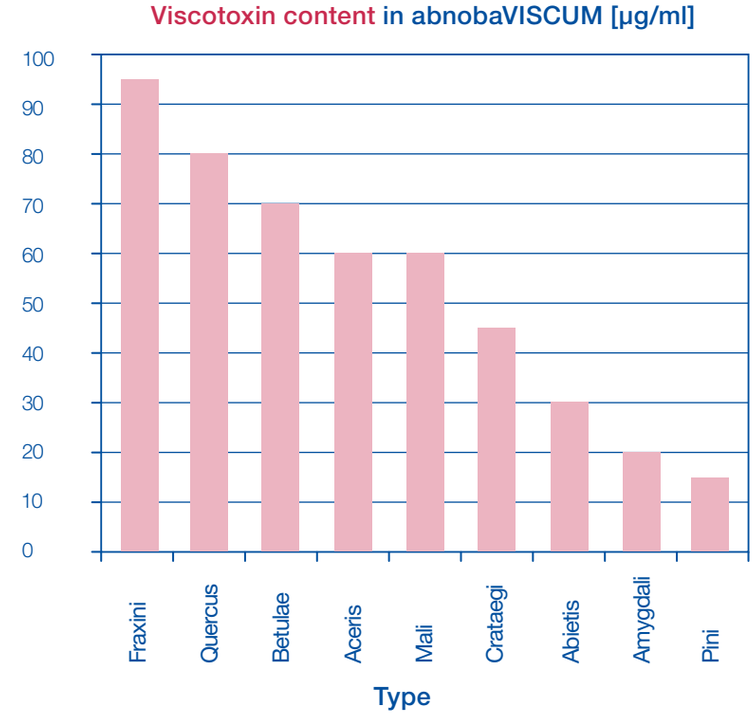

Figure 2: *Average total viscotoxin content of abnobaVISCUM preparations, strength 20mg, according to host tree (type).*

Specific features of abnobaVISCUM

abnobaVISCUM differs from other mistletoe preparations in the following ways:

- **Meticulous elimination of microbial decay**
  Standardized production at the harvest site prevents microbial spoilage and substance decay.
  Directly after harvesting mistletoe for abnobaVISCUM is stored in liquid nitrogen.

- **Active ingredients are not altered by oxidation**
  The entire abnobaVISCUM manufacturing process, from the storage of harvested plant materials to the final filling of ampules, takes place under inert gas so that oxidative changes (as evident in the brown colour of other similar preparations) cannot take place.

- **High mistletoe lectin and viscotoxin content**
  By means of the patented extraction process, 75 % of plant materials are retained in the extract solution. In this way it is possible to reliably achieve high concentrations of mistletoe lectins and viscotoxins in the extract. It should be emphasised that both substance groups can be equally well extracted.

- **Processing of liposomes**
  The natural liposomes contained in the extract explain why abnobaVISCUM is well-tolerated as a medicament and its high bio-availability.

- **Only for abnobaVISCUM**
  it is shown that mistletoe lectins are available in blood serum following subcutaneous administration.

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Recommendations for use of abnobaVISCUM

Therapeutic indications

- Relapse prophylaxis following tumour surgery.
- Treatment of malignant and benign tumour disease.
- Treatment of malignant disease of the haematopoietic organs.
- Treatment of defined pre-cancerous conditions.

abnobaVISCUM is administered as supportive treatment to chemotherapy and radiation therapy, and before and after surgery for reducing side effects and thus improving the patient's quality of life. Once standard therapies have been completed, abnobaVISCUM is administered as an immunomodulator for strengthening the organism overall and also as a prophylaxis against tumour recurrence.
Mistletoe therapy stimulates endorphine release and can help to reduce pain during advanced tumour stages. The symptoms of lack of appetite and disturbed sleep frequently occuring in connection with cancer diseases can also be relieved or eliminated.
Please refer to the section entitled "abnobaVISCUM in combination with other therapies" on page 29 for specific indications concerning supportive (adjuvant) treatment.

Contraindications

- In the case of acute infections or diseases accompanied by fever (body temperature above 38 °C), mistletoe treatment must be discontinued until the fever or infection subside.
- abnobaVISCUM should not be administered if there is any known hypersensitivity to mistletoe preparations.

Side effects

The following symptoms appear in almost all patients taking the correct "individual dosage":

Skin, cutaneous appendages:	Injection site inflammation up to 5 cm in diameter mostly appears 8 -12 hours after the injection; rarely after 24 hours
General:	Minor increase in body temperature within 12 hours following the injection
Blood and lymph system:	Temporary, minor swelling of nearby lymphnodes

The symptoms described above are harmless and present no cause for concern; they signal the patient's responsiveness to treatment. The minor increase in body temperature (up to 38 °C) triggered by abnobaVISCUM should not be suppressed with fever-reducing medicines or remedies.

Rare side effects:

Skin, cutaneous appendages:	Larger injection site inflammation over 5 cm in diameter, injection site nodule
General:	Pyrexia over 38 °C, fatigue, chills, malaise, headache, short spells of dizziness, triggering of inflammations
Blood and lymph system:	Injection site lymphadenopathy
Digestive tract:	Diarrhoea
Urogenital tract:	Increase urge to urinate

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The general symptoms described here do not indicate intolerance of the medication but rather that the dosage is effective. However, if these symptoms do not subside during the course of the day following the injection, or if the patient is unable to tolerate the symptoms, the dosage should be reduced to the next lowest strength. The next injection should only be given after the symptoms have subsided. A fever persisting for more than three days cannot be caused by a mistletoe injection and other causes should be investigated.

Very rare allergoid reactions:

Skin, cutaneous appendages:	Injection site or generalized urticaria, blistering, rash, erythema multiforme (one documented case), angioneurotic oedema (Quincke's oedema)
General:	Generalized pruritus, chills
Circulation system:	Anaphylactic shock
Airways:	Dyspnoea, bronchospasm

If any of these symptoms appear, discontinue administration of abnobaVISCUM immediately. Emergency medical measures should be taken with symptomatic treatment as described on page 39 in the chapter "Emergency treatment".

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If dosage is increased too rapidly, e.g. when a strength level is skipped, allergoid reactions requiring emergency medical treatment can result (see page 39). Becaue the symptoms described above are dosage-related and are not due to an allergy, treatment with abnobaVISCUM can be continued at a reduced dosage when the symptoms have subsided.

Use of abnobaVISCUM in patients with impaired renal or hepatic function

No restrictions for use. Long-term clinical experience provides no evidence for restricting administration of abnobaVISCUM to patients with limited kidney and liver function.

Pediatric use

abnobaVISCUM can be used in paediatric medicine. Extensive experience in this area shows no evidence of contraindications for children below the age of 12 years. Insufficient knowledge is available on administration to infants and toddlers under the age of 3 years.

Pregnancy and lactation

To date no effects are known to contraindicate administration of abnobaVISCUM during pregnancy. Particular caution should be exercised however, and therefore during the first three months of pregnancy, abnobaVISCUM should be administered strictly according to the prescribed indications. There is insufficient knowledge available to make recommendations for administration of abnobaVISCUM during breastfeeding.

Interactions with other medicinal products and other forms of interaction

· Interactions with other medicinal products and other interactions are unknown.

· Until now interactions with other immunmodulatory substances have not been investigated. Careful dosage and medical check-ups are recommended if such medication is administered within a short period of time after or before treatment with mistletoe preparations.

· Because of the parenteral application of abnobaVISCUM, an influence of foodstuffs on the effects of the preparation is unlikely and not known up to now.

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Choosing type of preparation (host tree)

The different types of abnobaVISCUM preparations (e.g. abnobaVISCUM Pini or abnobaVISCUM Fraxini) are distinguished by the trees upon which the mistletoe grows, the so-called “host trees”. Choosing the type of preparation depends on the kind of tumour and where it is located. Recommendations are described in the tabular summary (inside front page).

Dosage

abnobaVISCUM treatment starts at a low dosage which is **slowly increased over time**.

Increases in dosage and the frequency of administration are adjusted according to the individual patient’s responsiveness to the preparations. In this way dosage is gradually increased until the optimal dosage (individual dosage) is achieved.

Start of treatment

It is recommended that treatment starts with 1 ml (1 ampule) of 0.02 mg strength, injected 3 times per week. The treatment scheme provided (inside front cover) for increasing dosage is based on extensive clinical experience gained over many years. The reactions described in the section “Individual dosage” can be expected to arise frequently.

- If no reaction or a very minor reaction is observed after 8 injections of 0.02 mg strength, dosage can be increased to 0.2 mg strength, 3 injections per week.
- After a further 8 injections, if no reaction or a very minor reaction is observed, the dosage should be increased to 2 mg strength, 3 injections per week.
- If the reactions described in points (a) to (d) below are achieved at any stage, the dosage should be maintained until the reaction is no longer observed.

Individual dosage

The optimal individual dosage is reached when at least one of the following reactions is observed:

a) Injection site inflammation

An injection site inflammation mostly arises at the injection site within 8 to 12 hours; rarely only after 24 hours. This localized inflammatory skin reaction should be a maximum of 5 cm in diameter. It subsides within the next two to three days and becomes weaker during the course of treatment.

b) Body temperature response

Three types of body temperature response can be observed:

- Immediate response: Temperature increases during the course of the first 12 hours after the injection.
- Rhythmical response: The normal physiological temperature difference of 0.5 °C between morning and evening is recovered (page 37).
- Late reaction: During the course of the treatment the average body temperature level increases (page 37).

Temperature readings are taken rectally or orally. The first reading should be taken in the morning before getting out of bed, before 7^{00} h if possible; the second reading in the afternoon between 14^{00} h and 18^{00} h following a 30 minutes rest. The temperature readings should always be taken at the same time each day. The second reading should be taken at the point when the individual temperature is normally at its maximum. Experience has shown that the body temperature response (immediate response) disappears after several months of continual treatment with the same dosage concentration.

c) Immunological response

Stimulation of the specific and non-specific immune system. A positive immune system response can be shown by means of changes in the leukocytes, particularly through maturation and

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activation of lymphocytes and increase in eosinophiles.
An improvement of the cellular immune status can be observed through identifying lymphocyte sub-populations as well as by the number and activation of NK-cells.
These observable pharmacodynamic effects are dependent on the dosage strength at the start of treatment and change during the course of treatment. After 3 to 9 weeks, antibodies – mostly IgG-type – against mistletoe proteins (mistletoe lectins, viscotoxins) begin to appear.

d) Changes in general condition
Once the body temperature response subsides there is often an improvement in the patient's general physical and psychological condition. The patient often experiences increased sense of initiative, and in some cases pain reduction and appetite increase. It is possible to consider reducing the dosage of analgesics that have otherwise been necessary up to that point.

If one of the reactions described in points (a) to (d) is observed, the optimal individual dosage has been achieved. Some patients may only have one respone, i.e. temperature increase or a localized skin reaction, but most patients have a combination of all four reactions.
If none of the above reactions occur, the injection frequency can be varied or type (host tree) of abnobaVISCUM changed. (See indications for switching type of preparation on the inside front cover page)
It should be noted that localized skin reactions and temperature responses become weaker or disappear completely with continual treatment of the same dosage concentration.
The symptoms of fatigue, chills, malaise , headache and short dizziness that can arise on an injection day are not signs of intolerance; rather the symptoms indicate that the dosage is effective. However, if these symptoms do not subside during the course of the day after the injection, or if the symptoms become intolerable for the patient, the concentration or dosage should be reduced.
If the transition from one concentration to the next highest concentration results in an overshooting reaction, then the next administration of the new strength should only be half an ampule.*
If the patient already has strong reactions to 0.02 mg strength then D6 strength should be used. In cases of a strong reaction to D6 strength, then only one third of an ampule should be used; alternatively a different type (host tree) of abnobaVISCUM should be selected.

Different types of abnobaVISCUM preparation (i.e. produced from different host trees) of the same strength differ considerably in their quantitative composition. For example, abnobaVISCUM Fraxini contains about 50 times more mistletoe lectins than abnobaVISCUM Pini (see the section "Quality assurance", page 14/15, Figure 1 and 2). Therefore, when changing to a different type of mistletoe preparation, different reactions can be expected. For this reason the patient should re-start injections at a lower dosage or strength than they were using with the previous type.

If the patient's responsiveness changes during the course of treatment (for example, because of simultaneous chemotherapy or radiation therapy), the individual dosage should be determined anew.
In addition to assessing the patient's general condition, localized skin reactions and temperature responses, immunological parameters can be used to determine the patient's responsiveness to mistletoe therapy.

* *The contents of ampoules that have already been broken open should be disposed of and not used for a later injection.*

OVERDOSAGE

Increasing dosage in steps of more than one strength should be avoided. The procedure for determining the optimal individual dosage must be complied with.
A too-rapid increase in dosage, e.g. by skipping the next strength to the following one can lead to allergoid reactions requiring emergency medical treatment (see page 39). As the allergoid reaction is related to dosage (and not to an allergy as such), treatment can be continued at a decreased dosage when the symptoms have subsided.

Treatment duration and long-term therapy

Once the optimal individual dosage (see page 23) has been achieved, treatment can continue with 3 injections per week of this level of dosage. The overall duration of treatment is not restricted but should be determined by a physician. Risk of tumour recurrence and the patient's general condition are indicators for the length of treatment required.
The following approach is often used and serves as a suggestion:

- If the patient has a good general and psychological condition, after 2 years, frequency of injection can be reduced to 2 ampoules (2 injections) per week.
- If this frequency of injecting is maintained, in the 3rd year, treatment-free intervals of 1–3 weeks can be taken, up to a total of 3 months in that year.
- During the 4th year of treatment 2 treatment-free intervals of up to 3 months each can be taken, i.e. a total of 6 months in that year.
- From the 5th year onwards treatment can be limited to 3 months per year at the dosage level last used at the end of the 4th year.
- After 5-7 years in total (from the beginning of treatment) treatment can be discontinued if the patient's condition and prognosis are favourable.

Mistletoe therapy can be continued behond the 7th year, for example as a prophylaxis against tumour recurrence.

Treatment-free intervals

After a treatment-free interval lasting longer than 4 weeks, the patient should always begin injecting again with 0.02 mg strength following the process described in the section on "Individual dosage" (page 23)

Posology and method of administration

Subcutaneous injection

The recommended **injection site is under the skin of the abdomen**. The injection is given subcutaneously (i.e. into the fatty tissue under the skin) and the injection site should be varied if possible, e.g. alternating between the right side of the abdomen on one injection-day and the left side of the abdomen on the next injection-day*. Inflamed or infected areas of skin should not be injected, e.g. where there are localized reactions or lymphnodes. Areas that have received radiation therapy or the vicinity of operation scars should also be avoided. In these cases, subcutaneous injections can be given in the upper thigh or upper arm. It is recommended that the patient rests after the injection.

Intravenous Infusion

abnobaVISCUM D6 – D30 strength can be administered intravenously in special cases. Dosage and frequency depend on the physical condition of the patient and are determined individually.
The appropriate dosage of abnobaVISCUM combined with 250 ml

* *An information booklet about mistletoe therapy containing further instructions for subcutaneous injecting is available to patients and can be ordered from Abnoba GmbH free of charge.*

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saline solution is administered by intravenous infusion. The infusion should be administered over a period of at least 30 minutes. **(This only applies to D6 to D30 preparations. Higher strength "Off label use" infusions should be administered over a period of at least 120 to 150 minutes)**. If an allergoid reaction appears during the infusion, administration must be discontinued immediately. If the symptoms do not subside, emergency medical treatment must be given (see page 39).

Other types of administration ("Off label use")

If any of the following kinds of administration of abnobaVISCUM are being considered, we recommend initial consultation with our medical specialist services:

- Intravenous infusion with preparations of 0.02 mg to 20 mg strength.
- Instillation
  e.g. for malignant intrapleural effusion, bladder carcinoma, ascites.
- Treatment with higher first dosage
  e.g. for patients with good general condition who have not been treated with misteltoe preparations previously.
- Intratumoral injection
- Treatment for chronic hepatitis C

For Protocols contact us at:
Phone +49 (0)7231 - 31 50 50 Fax: +49 (0)7231 - 35 87 14
E-mail: info@abnoba.de

abnobaVISCUM in combination with other therapies

The patient's reaction to abnobaVISCUM injections can change during the course of radiation therapy, chemotherapy and following surgery. In rare cases it may be essential to re-establish the optimal individual dosage, starting injections with 0.02 mg strength once again (see page 22).

- Surgery
  Surgical interventions and anaesthetic drugs can have an immunosuppressive effect. Therefore it is recommended that abnobaVISCUM is given as an immunmodulatory medicine pre-operatively if possible, even if there is only a short period of time before the operation. The pre-operative treatment should start with 0.02 mg strength, 3 times per week. The mistletoe injections should be continued after the operation and until the wound has healed.

- Chemotherapy
  Treatment with abnobaVISCUM can reduce side effects of chemotherapy. Negative interactions between abnobaVISCUM treatment and simultaneous chemotherapy are not known. Clinical research has shown that quality of life improves when chemotherapy is accompanied by treatment with mistletoe preparations. When chemotherapy and mistletoe treatment are given simultaneously it is unlikely that mistletoe will have an immunomodulatory effect, i.e. that it will stimulate the immune system, because the immunosuppressive effect of chemotherapy is normally too strong. The main aim of mistletoe treatment in this case is to improve tolerance of chemotherapy and thus reduce side effects and improve quality of life. Dosage is determined according to the guidelines on page 22. If mistletoe treatment is started for the first time during chemotherapy, dosage should begin at a low level and should be increased very gradually and carefully over time.

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- Radiation therapy
  abnobaVISCUM can be administered during radiation therapy, although the areas of the body and skin that have been treated should be strictly avoided as injection sites. In some cases it can become necessary to reduce dosage because of changes in the patient's reactions (especially where there is a tendency to inflammatory reactions).
- Hormone treatment
  abnobaVISCUM can also be administered simultaneously with hormone treatment. Any changes in the patient's reactions to the mistletoe preparations, however, should be taken into account.

Ampoules:
Indications for handling, storage and transport

abnobaVISCUM preparations have been protected from oxidation under the strictest conditions during the entire manufacturing process. For this reason, injections must be given immediately after breaking open the ampoules; the contents of opened ampules cannot be used at a later time.

Ampoules containing brown-coloured liquid may not be used as this indicates that the preparation has been exposed to oxygen and spoiled. abnobaVISCUM 20 mg to 0.02 mg strengths must be stored in the refrigerator (2 to 13 °C). The ampoules may not be frozen. If ampoules are transported, e.g. from the pharmacy to the patient's home, continual cooling at the abovementioned temperatures is not necessary. However, extreme temperatures such as frost or heat (over 25 °C) should be avoided.

There are no particular storage recommendations for abnobaVISCUM D6 to D30 strengths. These ampoules do not have to be kept in the refrigerator, although they should not be stored or transported at temperatures above 25 °C.

Preclinical investigations

Pharmacology and toxicology studies were carried out for abnobaVISCUM Fraxini 20 mg in 2002, in accordance with the GLP. As this particular type of preparation (host tree) and strength contains the highest content of pharmacologically effective substances, e.g. mistletoe lectins and viscotoxins, it was considered to be representative of all the other preparations for the purposes of these studies.

The following pharmacological safety studies using animals were carried out for abnobaVISCUM Fraxini 20 mg:

- Effect on breathing and cardiovascular system.
- Effect on water and electrolyte metabolism.
- Effect on the central nervous system.

An effect on these secondary pharmacological parameters was only observed once the clinical human dosage was increased by more than 50 times.

The following toxicity studies were carried out:

- Acute toxicity following subcutaneous and intravenous administration.
- Embryotoxicity following repeated subcutaneous administration.

Studies on acute toxicity indicated that there is a wide spectrum for clinical administration to the human being, both for intravenous and subcutaneous administration. The embryotoxicity studies showed no teratogenic effect.

The mutagenicity (genotoxicity) of abnobaVISCUM was tested in-vitro (Ames assay and structural chromosomal aberrations test for human lymphocytes) and in-vivo (micronucleus test). The studies gave no indication of mutagenic potential.

The toxological studies gave no indication of carcinogenic potential. Studies concerning local tolerance of anobaVISCUM in intrapleural applications showed excellent intrapleural tolerance.

RECOMMENDATIONS FOR USE

Thus pre-clinical data obtained through standard safety studies of acute toxicity, reproduction toxicity and genotoxicity show no particular danger for the human being. Both pre-clinical and clinical pharmacokinetic studies show good biological availability of typical mistletoe substances (e.g. mistletoe lectins, viscotoxins) following subcutaneous injection. Hence, within the context of the abovementioned embryotoxicity study, viscotoxins were found in rat serum.
Once sufficiently sensitive analytical tools became available for mistletoe lectins, an analysis of the serum of test subjects and patients showed that mistletoe lectins were also systemically available following subcutaneous administration of abnobaVISCUM.

Pharmaceutical information

Incompatibilities:	Not known.
Shelf life:	abnobaVISCUM 20 mg to 0.02 mg has a shelf life of 3 years. abnobaVISCUM D6 to D30 has a shelf life of 5 years.
Storage conditions:	abnobaVISCUM 20 mg to 0.02 mg strengths should be stored in the refrigerator (2 - 13 °C). Do not freeze. abnobaVISCUM D6 to D30 strengths: Do not store over 25 °C. The changed and new storage recommendations (since 2008) are based on new research methods and research results. The results are also showing that cooling during transport is not necessary.
Type of container and content:	abnobaVISCUM is available in breakable glass ampoules, each containing 1 ml of injection solution. The 20 mg und 2 mg strengths are yellow-green in colour. All other strengths are colourless.
Indications for handling:	The contents of ampoules that have been opened may not be used for an injection later on. Ampoules containing brownish coloured liquid should not be used - this indicates that the preparation has been exposed to oxygen and has been spoiled.

The information provided in this brochure was updated in ***2009***

Expert Information*

1 Name of the medicinal product

abnobaVISCUM®

differentiated according to the mistletoe host trees: (Abietis) fir, (Aceris) maple, (Amygdali) almond, (Betulae) birch, (Crataegi) hawthorn, (Fraxini) ash, (Mali) apple, (Pini) pine and (Quercus) oak, in the concentrations 20 mg, 2 mg, 0.2 mg, 0.02 mg, D6, D10, D20, D30, complete name e.g.: abnobaVISCUM Abietis 20 mg or abnobaVISCUM Abietis D6.

Active substance:
a) Pressed juice from mistletoe herb from the respective host tree (20 mg – 0.02 mg),

and

b) Viscum album of the respective host tree ex herba recente col. D6, D10, D20, D30.

2 Prescription status/Legal category

Pharmacy-only medicine

3 Composition of the medicinal product

3.1 Substance or indication group

Anthroposophical medicinal product

3.2 Pharmaceutically active constituents, qualitative and quantitative

a) For the concentrations 20 mg to 0.02 mg a concentrated pressed juice which contains 75% of the mistletoe material used. This yields the composition of the concentrations 20 mg to 0.02 mg as follows:

1 ampoule of 1 ml solution for injection contains in

20 mg: 15 mg pressed juice from 20 mg mistletoe herb of the respective host tree

2 mg: 1.5 mg pressed juice from 2.0 mg mistletoe herb of the respective host tree

0.2 mg: 0.15 mg pressed juice from 0.2 mg mistletoe herb of the respective host tree

0.02 mg: 0.015 mg pressed juice from 0.02 mg mistletoe herb of the respective host tree

b) For the concentrations D6, D10, D20 and D30 the following applies:

1 ampoule of 1 ml liquid dilution for injection contains in

D6: Viscum album of the respective host tree ex herba recente col.
D6: 1 ml

D10: Viscum album of the respective host tree ex herba recente col.
D10: 1 ml

D20: Viscum album of the respective host tree ex herba recente col.
D20: 1 ml

D30: Viscum album of the respective host tree ex herba recente col.
D30: 1 ml

3.3 Excipients

Concentrations 20 mg, 2 mg and 0.2 mg: disodium hydrogen phosphate $2\,H_2O$, ascorbic acid, water for injections

Concentration 0.02 mg: disodium hydrogen phosphate $2\,H_2O$, sodium dihydrogen phosphate $1\,H_2O$, ascorbic acid, water for injections
D6, D10, D20 and D30: no excipients

4 Therapeutic indications

According to the anthroposophical understanding of man and nature, including:
treatment of malignant and benign tumours; treatment of malignant disease of the haematopoietic organs; treatment of defined precancerous conditions; prevention of relapse after oncological surgery.

5 Contraindications

In acute inflammatory or febrile illness (body temperature above 38°C), treatment should be interrupted until the fever and/or inflammation begin to subside. Do not use in known hypersensitivity to mistletoe preparations. Insufficient experience is available for use in infants and toddlers.

To date no effects have been reported that argue against the use of mistletoe products during pregnancy. For reasons of particular caution mistletoe products should only be used during the first three months of pregnancy if strictly indicated.

6 Undesirable effects

Slight rise in body temperature, local inflammatory reactions around the subcutaneous injection site as well as slight transient swelling of regional lymph nodes are normal. The fever caused by abnobaVISCUM should not be suppressed by use of antipyretic agents. In fever lasting longer than three days the differential diagnoses infectious process or tumour fever must be considered. If the reactions exceed a tolerable level or a level desired by the doctor (fever above 38°C, tiredness, shivering, general malaise, headache, transient dizziness, diarrhoea, increased micturition urge, fatigue, larger local reactions above 5 cm in diameter), the next injection should only be given after these symptoms have regressed and the concentration and/or the dose should be reduced.

In rare cases there may be subcutaneous nodular infiltration at the injection site, increased swelling of the regional lymph nodes and activation of inflammations.

In case of rare allergic or allergoid reactions such as generalised itch, local or generalised urticaria, blister formation, exanthema, erythema exsudativum multiforme (one documented case), Quincke's oedema, chills, dyspnoea, bronchospasm and shock the preparation must be discontinued immediately and medical treatment is required.

7 Interactions with other medicinal products

No interactions with other medicinal products are known.

8 Warnings

No information planned.

9 Most important incompatibilities

No interactions with other medicinal

10 Posology with individual and daily doses

Unless otherwise directed, dosage is always 1 ml solution for injection of the given dilution. Treatment should begin with a concentration of 0.02 mg, three times weekly. The concentration

** in accordance with section 11a of German Drug Law*

is then carefully increased until the optimal dose is reached. The dosage should always be established on an individual basis in accordance with patient response.

Determining the individual dose

The individual dose is that at which the patient shows at least one of the following responses:

a) Change in subjective condition

Improvement in general condition and psychological state, increased initiative and possibly pain relief indicate that the chosen regimen is within the effective dose range. Any tiredness, shivering, general malaise, headache and transient dizziness on the day of injection are not signs of intolerance but show that the dosage administered was effective, possibly too high. If these symptoms have not subsided on the day after the injection or if they become intolerable, the concentration and/or the dose should be reduced.

b) Local inflammatory response

This should not be more than 5 cm in diameter.

c) Temperature response

Since the desirable temperature responses during therapy are important for evaluating the course of treatment the patient should be instructed to keep a basal temperature graph. Please note the following:

The temperature should be measured rectally or orally. The first measurement should be made in the morning before rising, preferably before 7 a.m. The second measurement should be made in the afternoon between 2 p.m. and 6 p.m. after the patient has been lying down for half an hour. The temperature should always be taken at the same time of day. The second measurement should preferably be taken at the time of the individual maximum temperature.

If it necessary to determine the individual maximum temperature then the temperature should be taken regularly over the course of one day. It should be measured every two hours between 7 a.m. and 9 p.m. after the patient has been lying down.

Three types of temperature response are observed:

1. Immediate response: a single rise in temperature after the injection.

2. Rhythmical response: restitution of the physiological morning/evening temperature difference of at least 0.5°C (Fig. 1).

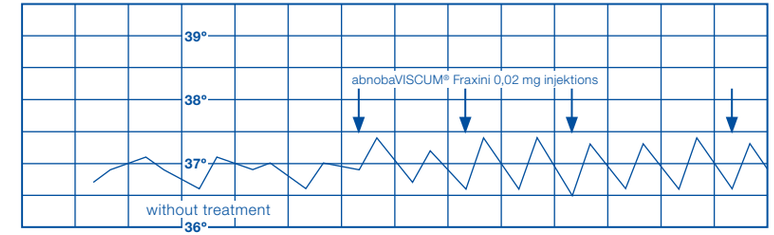
3. Delayed response: in the course of treatment the mean temperature increases. In such cases the subfebrile range must also be monitored (Fig. 2).

In some patients only one temperature response is observed. However, in most cases combinations of the three types of response can be observed.

d) Immunological response

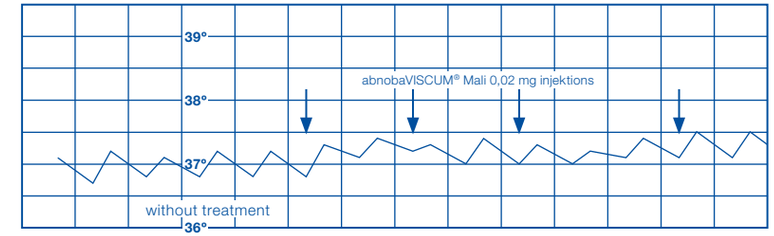
For example, increased leukocytes (above all the absolute lymphocyte and/or eosinophil count). Improvement of the cellular immune status in the Multitest Mérieux® or by counting the lymphocyte subpopulations.

The individual dose may already be reached at a concentration of 0.02 mg.



Example for temperature response

Fig. 1: Rhythmical response



Example for temperature response

Fig. 2: Late response

Otherwise the concentration should be increased incrementally to 0.2 mg, 2 mg and 20 mg with 3 injections of each weekly. As severe responses may occur when changing from one concentration to the next higher one, only ½ ampoule of the next higher concentration should initially be injected.

If excessively severe responses already occur at a concentration of 0.02 mg, a change should be made to D6. If excessively severe responses also occur at this dilution level, only one third of the ampoule should be used or a change made to dilution level D10 or to abnobaVISCUM from another host tree.

If none of the responses listed above can be achieved, the following may be tried:

- change in injection frequency
- a change can be made to abnobaVISCUM obtained from another hosttree.

In case of tumour fever – also in the sense of B symptomatology with lymphomas – low concentrations are given with the aim of normalising the core temperature and restoring a physiological rhythm. In such cases assessment of the course of the disease is based on the local inflammatory reactions, the general state of health and the standard oncological criteria.

Continuing therapy

The individual dose (see above) should

be brought into a rhythm using weaker concentrations. For example, if the individual dose is with concentration 2 mg, then concentration 2 mg can be administered on Mondays, and the concentration 0.2 mg on Wednesdays and Fridays.

If the patient's response situation changes during the course of treatment, the individual dose must also be reassessed. In addition to the patient's general condition and local and temperature responses, immunological parameters can also be used to assess responsiveness.

During radiotherapy or chemotherapy and after surgery, the patient's individual response may change and the dose may have to be readjusted.

After any breaks lasting more than 4 weeks the initial dose should be halved when resuming therapy.

Posology in impaired renal function

As described above. There are no restrictions on use.

11 Method and duration of administration

Method:

Subcutaneous injection
In special cases the required dose of concentrations D6 to D30 can be mixed with a solution for infusion (physiological saline or 5% glucose solution) and administered by slow i.v. infusion. The infusion of 250 ml should last for at least 30 minutes. In the case of malignant effusions the infusion may be given directly into the affected body cavity after the required puncture.
Since the preparations are produced under strict oxidation protection they must be injected immediately after opening the ampoule. Any opened ampoules must be discarded immediately.

Site:
Wherever possible inject near to the tumour or metastases, a different injection site should preferably be chosen at every administration (various sites in the abdomen, thigh or upper arm). Injections into inflamed skin areas (e.g., local response) or irradiation fields should be avoided. Strictly observe subcutaneous injection technique.

Time:
Whenever possible the injections should be given in the morning during the temperature increase phase. Patients are recommended to rest afterwards.

Duration:
There is basically no limit to the duration of treatment. It will be decided upon by the clinician, based upon the risk of tumour recurrence, the individual findings, and the patient's condition. If the patient's condition is stable, a dose reduction to two ampoules a week can be made after two years. After three years, treatment breaks of four weeks can be made after each eight weeks' therapy. After each treatment break therapy must be started with the induction therapy as given in the dosage instructions. After seven years if the course remains unsuspicious therapy with abnobaVISCUM may be discontinued. During times of psychological and physical stress, particularly with intercurrent viral illness, patients require closer monitoring. It is essential to continue treatment during holidays or while travelling.

12 Emergency measures, symptoms and antidotes

Degree of severity I

Severe skin reactions, urticaria etc.

subside without further treatment within two days of discontinuing the product.

Chills

subside without further treatment within two days of discontinuing the product.

Degree of severity II

Dyspnoea

subsides after a few minutes In most cases.

Otherwise antihistamines should be used. If there is insufficient response, intravenous corticosteroids, e.g., 100 mg prednisolone, should be administered.

Degree of severity III

Shock

requires the following sequence of medication and dosages:

1. Adrenaline 0.05 – 0.1 mg i.v., i.e., 1 ml Suprarenin 1:1000 diluted with 9 ml physiological sodium chloride solution, of which 0.5 – 1 ml is given as a slow intravenous administration. This dose is repeated after 1 – 2 minutes, depending upon the response and the patient's condition. Blood pressure values and, in particular, cardiac action (arrhythmias) must be closely monitored.

2. Intravenous corticosteroids, e.g., prednisolone, at a dose of at least 500 to 1000 mg.

3. As volume substitution, 5% albumin solution. In a severe incident, the sequence outlined here, first adrenaline, then corticosteroids, is recommended because an immediate effect can only be achieved with adrenaline.

The corticosteroids suggested for administration in second place, at the given high dose, require 5 – 10 minutes until their onset of action and this period has to be bridged by the effect of adrenaline.

In addition to this medicinal therapy, further measures such as patient positioning, ventilation and cardiac massage may, of course, be indicated depending upon the clinical picture.

13 Pharmacological and toxicological properties

Cancerostatic and immunomodulating properties of Viscum album total extracts have been described in vitro, in laboratory animals and in humans. Animal investigations of acute and subacute toxicity show a good therapeutic range of the preparations used. Tests on bacterial strains (Ames salmonella / microsome plate incorporation assay) gave no indication of mutagenicity. Investigations of chronic toxicity, reproduction toxicity and cancerogenicity are not available. Investigations of pharmacokinetics and bioavailability have not been conducted for methodological reasons.

14 Other information

The concentrations 20 mg and 2 mg are coloured green-yellow.

15 Shelf life

Concentrations 20 mg, 2 mg, 0.2 mg and 0.02 mg: The preparations have a shelf life of three years when stored between 2°C and 13°C. The preparation should be used immediately after opening the ampoule.

Concentrations D6, D10, D20 and D30: The preparations have a shelf life of five years when stored normally. The preparation should be used immediately after opening the ampoule.

16 Special precautions for storage

Concentrations 20 mg, 2 mg, 0.2 mg and 0.02 mg: Store at 2 – 13°C. Do not freeze.

Dilution level D 6 – D 30: None required.

17 Pharmaceutical forms and pack sizes

All AbnobaVISCUM® preparations:
Pack with 8 ampoules of 1 ml solution for injection or liquid dilution for injection. Pack with 48 ampoules of 1 ml solution for injection or liquid dilution for injection.

Concentrations 20 mg to 0.02 mg:
Pack with 21 ampoules of 1 ml solution for injection

18 Date of revision of text
August 2007.

18 Name or company and address of the marketing authorisation holder

ABNOBA GMBH
Hohenzollernstr. 16
75177 Pforzheim
Telephone +49 (0)72 31- 31 50 50
Telefax +49 (0)72 31- 35 87 14

Selected literature for further reading

For Healthcare Professionals

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For further literature and information regarding specific forms of treatment our Research Departement can be consulted

Please contact us at:
Phone +49 (0)7231 - 31 50 50 Fax: +49 (0)7231 - 35 87 14
E-mail: info@abnoba.de

Websites:

www.abnoba.de English language available
www.mistel-therapie.de (www.mistel-therapie.de/mistletoe.html)

Selected literature for further reading

For Patients

Our patient brochure is also available in Dutch, German, Spanish and Turkish.

We would be grateful to receive your criticisms and suggestions for improvement of this brochure.