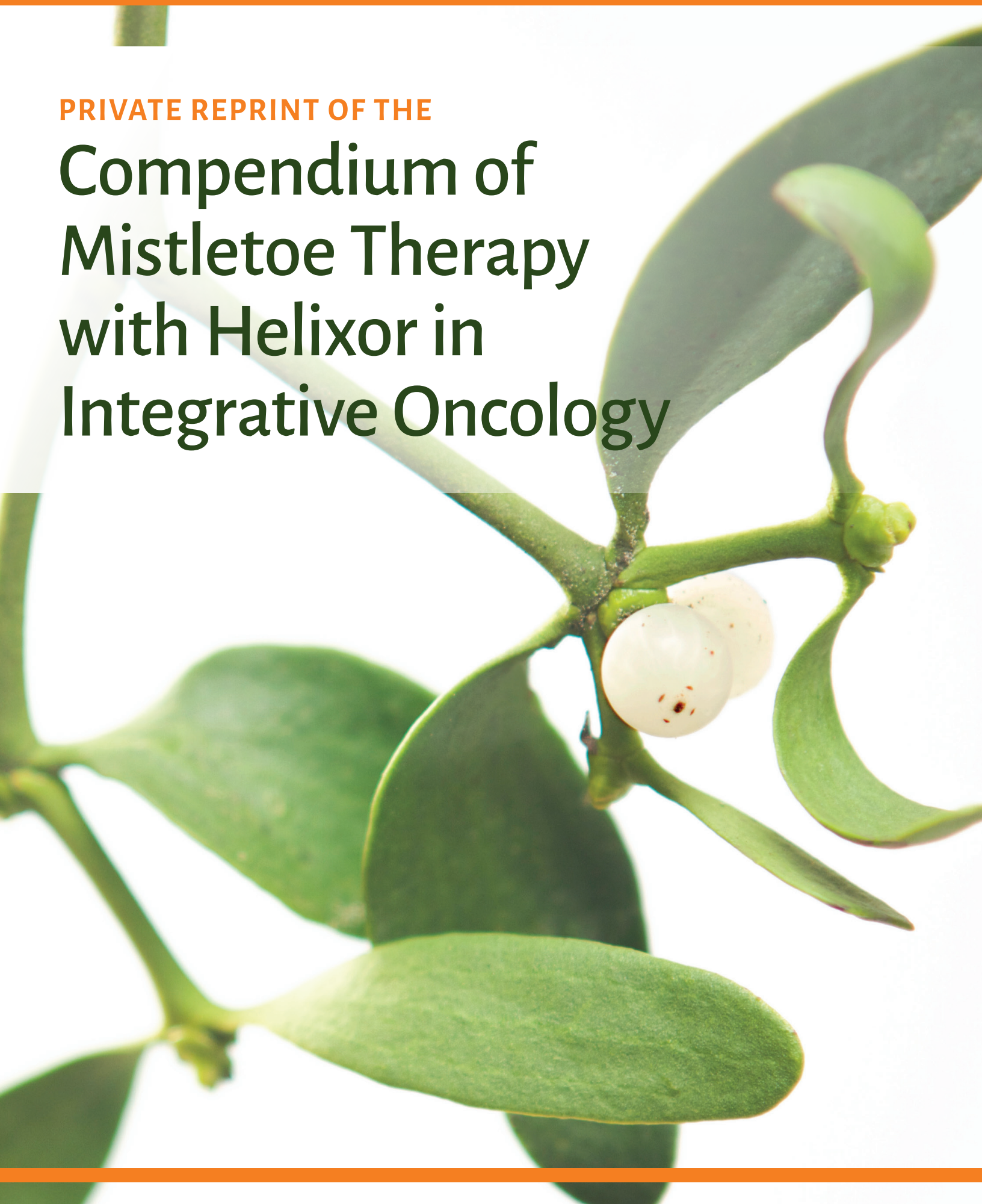
PRIVATE REPRINT OF THE

Compendium of Mistletoe Therapy with Helixor in Integrative Oncology



Introduction

Mistletoe therapy is an integral part of integrative oncology.
This compendium on Helixor® therapy is based on the insights and experiences from over 40 years of mistletoe research and therapeutic use.

Here you will find practice-oriented, general therapeutic principles and specific treatment schedules for the most frequent tumor entities.

Depending on Helixor®'s regulatory status not all of their products are available in every country.

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Composition

Helixor® is a composition of purely aqueous fresh plant extracts from the white-berry mistletoe (Viscum album L.). It is produced using special rhythmic flow methods developed by Helixor® and without using fermentation. Sterility is ensured through sterile filtration. No additives (preservatives or similar) are added, with the exception of sodium chloride for isotonization and sodium hydroxide for adjusting the pH value. The entire manufacturing process is standardized and complies with the guidelines of the European Union for "Good Manufacturing Practice" (EU GMP Guidelines).

The quantity of fresh plant used for the production of an ampoule of aqueous extract is given in mg (for example, 100 mg of fresh plant fir mistletoe are used to produce a single ampoule of Helixor® A 100 mg).

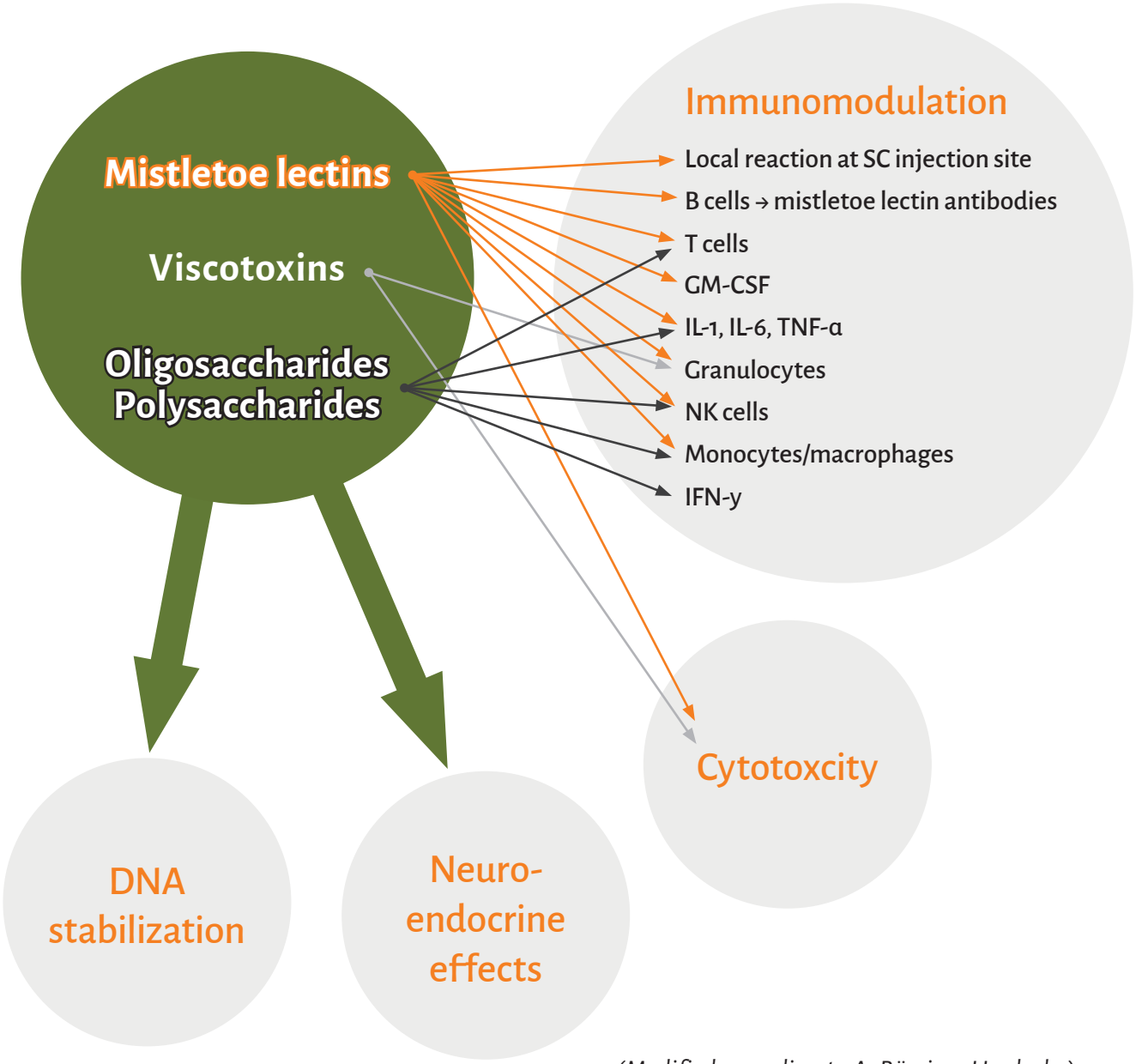
Ingredients of Mistletoe Extracts

Structural Types	Classes of Substances	Effects on Tumor Cells	Effects on Immune Cells
Glycoproteins	Mistletoe lectins I, II, and III (RIP II)	Cytotoxicity through inhibition of ribosomal protein synthesis + induction of apoptosis (intrinsic pathway)	Macrophage activation, release of TNF -α, IL-1, IL-2, IL-8, eosinophilia
	VisalbCBL = cbML	Weak cytotoxicity	Adjuvant increase in immune response
Polypeptides	Viscotoxins A_{1-3}, B_1, 1-PS, U-PS	Cytotoxicity through cell membrane leakage	Macrophage activation, increased phagocytosis activity of granulocytes
Oligo- and polysaccharides	Arabinogalactans, galacturonans	Indirect, immune-mediated tumor inhibition	Stimulation of T-helper cells (TH1 ↑, IFN-γ ↑), increased NK cell activity
Flavonoids	Quercetin derivatives	Induction of apoptosis	Antioxidant, anti-inflammatory + antinociceptive effects
Phenylpropane glycosides	Syringin	-	Stress protection and immunoprotection (adaptogenic), antioxidant
Triterpenes	Oleanolic, ursolic, betulinic acid	Induction of apoptosis and cell differentiation, antiangiogenesis	Anti-inflammatory + antioxidant effects, immunoprotection

Composition (cont.)

According to current scientific knowledge, mistletoe extracts must be regarded as natural multi-substance mixtures. Biological activity and synergy relating to antitumoral effects have not only been published for mistletoe lectins and its fragments, but also for viscotoxins, oligo- and polysaccharides, amino acids, flavonoids and triterpenes.

The whole plant extract is the active substance of the mistletoe



(Modified according to A. Büssing, Herdecke)

Only the whole plant extract in its complexity is able to achieve the complex effects.

Mistletoe Host Trees and Dosing Form

Series Boxes:

Series 1	7 x box
1 mg	3 ampules
5 mg	3 ampules
10mg	1 ampule

Series 2	7 x box
10 mg	2 ampules
20 mg	2 ampules
30 mg	3 ampules

Series 3	7 x box
1 mg	1 ampule
5 mg	2 ampules
10 mg	3 ampules
20 mg	1 ampule

Series 4	7 x box
20 mg	2 ampules
30 m g	2 ampules
50 mg	3 ampules

Helixor® A (Abietis) made from fir mistletoe

Helixor® M (Mali) made from apple tree mistletoe

Helixor® P (Pini) made from pine mistletoe

Single Strength Boxes:

1 mg	8 x box
5 mg	8 x box
10 mg	8 x box
20 mg	8 x box
30 mg	8 x box
50 mg	8 x box
100 mg	8 x box

Shelf Life

Helixor products are best preserved stored in a cool, dry place away from direct sunlight. While refrigeration is not required, after 2-year qualitative studies it will not adversely change the product and may offer some small benefit over time.

Recommended shelf life of Helixor Mistletoe is 2 years after purchase. Especially in higher milligram concentrations.

Mode of Action

Mode of Action of Mistletoe Therapy

Stimulation of salutogenesis and self-regulation in cancer patients. Among others, this manifests itself by:

- Local inflammatory reaction at the SC injection site
- Temperature reaction, improved internal warming
- Increase in leukocytes (neutrophils, eosinophils, lymphocytes)
- Acute peritumoral inflammatory reaction
- Restoring physiological rhythms, for example, sleep-wake cycle

Overview of the Pharmacological Effects of Helixor®

Effects	Clinical Relevance
Immunomodulation	Reduced susceptibility to infections, indirect immune-mediated tumor inhibition
Immunoprotection (DNA stabilization)	Better tolerability of chemotherapy, less immunosuppression by chemotherapy
Neuroendocrine effects	Improved quality of life (especially fatigue)
Tumor inhibition (apoptosis ↑, angiogenesis ↓)	Prolongation of survival time, tumor regression in specific cases

Immunological Effects of Subcutaneous Injections of Helixor®

A major part of the clinical effects of subcutaneous Helixor® injections can be explained by proven effects on the communication network within the immune system.[4, 6, 29, 100, 122, 125, 127, 128, 133, 136, 138, 139, 142] (See Fig. 1 below)

The binding of mistletoe substances to the cell membrane [57, 97] initially activates immune cells in the skin. This leads to a number of subsequent reactions.

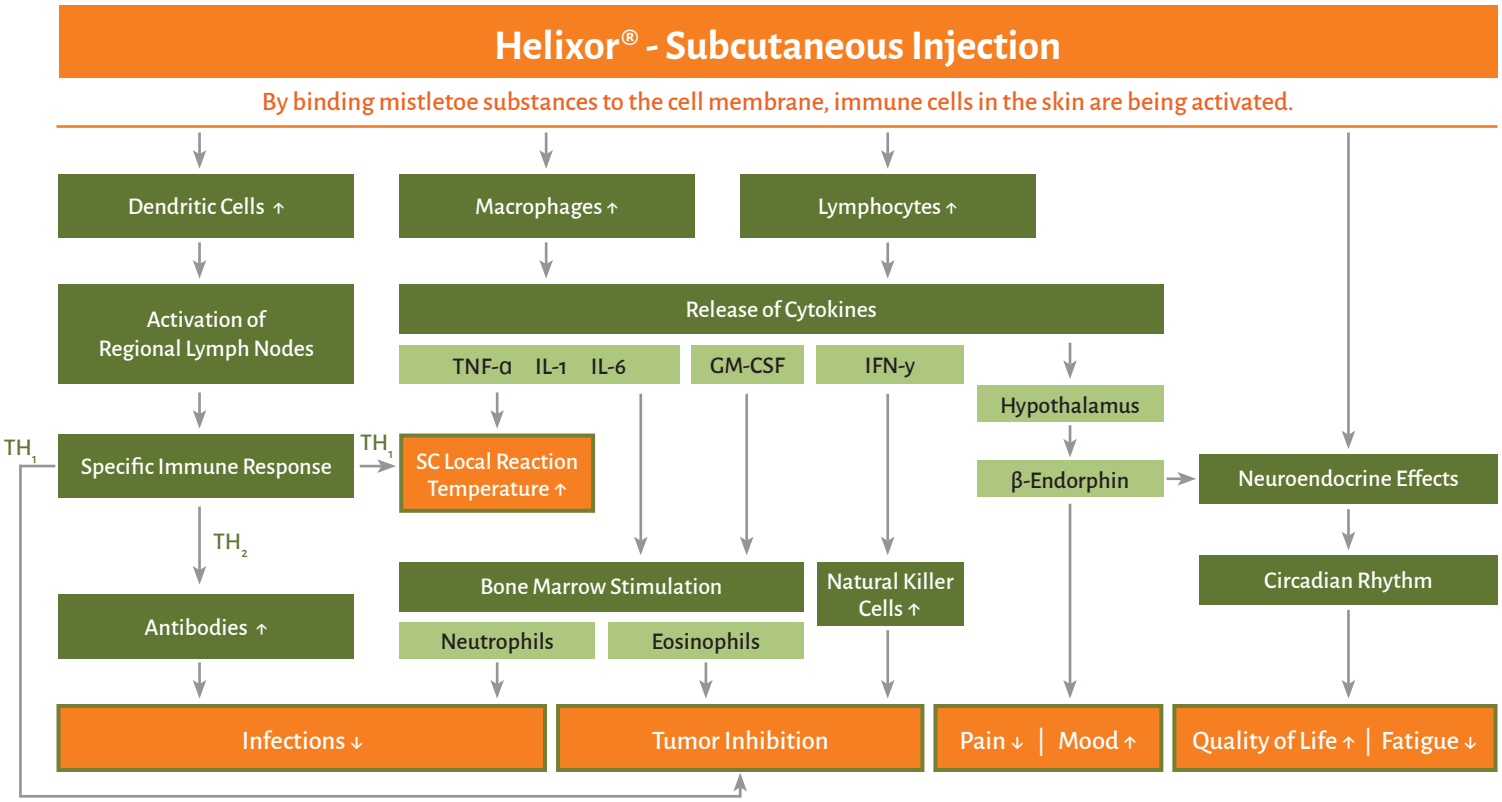
Therapeutic Indications

- Malignant tumors, also with concomitant disorders of the hematopoietic system
- Relapse prevention following tumor surgery
- Defined precancerous conditions (e.g. .cervical intraepithelial neoplasias, chronic hepatitis B and C, colitis ulcerosa, intestinal polyps)
- Benign tumors (e.g. uterine myomas, endometriosis, brain tumors)

The use of mistletoe products is restricted to adults.* However, good results have been observed in children and adolescents with Helixor® A.[82, 130, 132]

* Depending on Helixor®'s regulatory status this may differ from country to country.

Fig. 1



Contraindications

Allergies to mistletoe preparations

Although most cases are dose-dependent pseudoallergies, it's not recommended to continue treatment for reasons of safety.

Acute inflammatory respectively highly febrile diseases (fever over 38 °C =^ 100.4 °F)

These may be exacerbated by mistletoe therapy and require a treatment pause until the symptoms subside.

Florid autoimmune diseases and those under immunosuppressive therapy

As soon as the patient has stabilized and no longer requires immunosuppressive therapy, mistletoe therapy can be administered using careful dosing.

Hyperthyroidism with tachycardia

Here, Helixor® can exacerbate the clinical symptoms. It can be administered again once tachycardia has normalized. Hyperthyroidism based purely on lab values and without clinical symptoms is not a contraindication!

Special Warnings and Precautions

In allergic patients, meticulous attention should be paid to dosing and diligent monitoring of reactions. In severe cases begin with Helixor® A 0.01 mg*, in milder cases with 0.1* or 1 mg: In all cases however, use a gradual increase in dose using original packs. The reason for this is that more excessive reactions to mistletoe injections occur, partly in form of generalized allergic reactions, in patients with an allergic diathesis. In patients with latex allergies or allergies to certain tropical fruits (such as kiwi, avocado and bananas), one should also consider cross-allergies with the chitin-binding mistletoe lectin (VisalbCBL) contained in mistletoe products.

In primary brain and spinal cord tumors or brain metastases with the risk of increased intracranial pressure, the indication of Helixor® must be handled very carefully, providing an adequate antiedematous treatment and close clinical supervision.

Caution is required for administration during pregnancy and lactation as no appropriate studies in animals are available regarding the effects on pregnancy and infant development, and the potential risk for humans is unknown.

Adverse Reactions

Local inflammatory reactions at the injection site

More or less pronounced local inflammatory reactions can be expected during the initial stage of treatment at the subcutaneous injection site. These are desirable and only to be regarded as adverse reactions if they exceed a diameter of 5 cm.

Local reactions are not a sign of intolerability or allergy. The following table is a useful aid to differential diagnosis.

Differential Diagnosis	
Local Inflammatory Reaction	**Localized Allergies**
Size can be controlled by dose	No dose dependence
Gradual decrease during maintenance therapy up to complete disappearance	Increase from injection to injection (despite significant dose reduction)
Negligible pruritus	Pronounced pruritus, tending towards generalization

Fever and flu-like symptoms

A slight increase in body temperature between 0.5 – 1 °C (^= 0.9 – 1.8 °F) 4 – 12 hours after the injection is a desired reaction[81] and is generally also regarded as pleasant by the patient.

Even fever can be a desired reaction, if it is purposely induced as part of fever therapy (active hyperthermia) to stimulate an antitumoral immune response (see page 66).
In the subcutaneous injection of Helixor® this is normally only possible by using higher doses. In conventional therapy initiation with 1 mg, fever and flu-like symptoms (including shivering, chills, fatigue, malaise, muscle and limb pains, headaches, dizziness) only occur in sensitive patients or too-rapid increases in dose. These subside again after 1 – 2 days. If possible the fever caused by Helixor® should not be suppressed with antipyretics.

If fever is not desired (weaker patients, or for example during chemotherapy) and flu-like symptoms still persist on the next morning, then a therapeutic pause should be maintained until the symptoms subside, followed by a dose reduction (also see page 35).
If fever persists for more than three days, one should determine whether latent or chronic infections have been activated by the therapy and require targeted treatment (dental foci, sinusitis, cholecystitis, urinary tract infections, etc.). In differential diagnostic terms, one should also consider tumor fever. A therapy pause is indicated in case of concomitant infections with fever over 38 °C (=^ 100.4 °F).

Allergic Reactions

Localized or general allergic reactions may occur occasionally. These occur most frequently as generalized pruritus, urticaria or maculopapular exanthema, more rarely as Quincke's edema or bronchospasm, and only in individual cases as erythema exsudativum multiforme or shock (the latter has so far not been observed with the proper use of Helixor®).

Rare Adverse Reactions

Regional swelling of lymph nodes

Transient enlargement of regional lymph nodes in the drainage area of the injection site is rarely observed. An activation of the dendritic cells (Langerhans' cells) in the skin as a result of the subcutaneous injection of Helixor® by necessity leads to a migration of these cells to the regional lymph nodes with activation of the T helper cells and other immune cells. This is a precondition for the specific humoral and cellular immune reactions to mistletoe antigens[138] regularly observed with subcutaneous mistletoe therapy. Therefore, the regional swelling of the lymph nodes is a desired effect, although this activation generally lies below the perception threshold.

This is a transient event with complete involution and generally occurs within a few days with a pause in Helixor® therapy or a change of injection site.

Activation of pre-existing inflammation

In rare cases, the injection of Helixor® can also lead to an activation of inflammatory processes through the release of proinflammatory cytokines. Reactivation of a previous local reaction site is the most commonly observed inflammatory reaction, especially with high-dose intravenous infusion. The activation of chronic inflammatory dental foci and eczemas has also been described. As a prophylactic measure against these adverse reactions it is recommended to observe the contraindications for acute inflammatory diseases and to avoid injecting near inflamed skin areas or inflamed superficial veins.

Chronic granulomatous inflammation and autoimmune diseases

The occurrence of chronic granulomatous inflammation (sarcoidosis: 3 cases; erythema nodosum: 2 cases) and of autoimmune diseases (dermatomyositis: 1 case) have been reported with mistletoe therapy.

Increased intracranial pressure in brain tumors or brain metastases

Symptoms of increased intracranial pressure in brain tumors or brain metastases have also been reported with mistletoe therapy. After initiating adequate antiedematous therapy, higher doses of Helixor® were well tolerated without signs of intracranial pressure.

Allergic Reactions Procedure

1. In case of a documented clinical allergic reaction, discontinue mistletoe therapy with Helixor®.

2. In cases of uriticaria, Quincke's edema, dyspnea or anaphylaxis, follow medically-approved emergency procedures for your country. Any clinical application of Helixor® outside of sub-Q and oral delivery should *only* be performed and supervised by trained clinicians in a clinical setting, appropriate to handle emergency situations and allergic reactions of all types.

3. Allergic reactions to Helixor ® are rare. However, in European clinical settings the unusual reactions encountered respond to typical treatment including volume expansion, Catecholamines, Clucocorticoids, Histamine antagonists, and Theophylline.

Interactions with Other Drugs

Please observe the following rules:

- Exercise caution during simultaneous use with other immunomodulating substances (e.g. thymus extracts, interferons, BCG) to avoid additive or over-additive effects (careful dosing and meticulous immune monitoring).

- Helixor® should not be drawn into a syringe with other drugs as precipitation or impaired effectiveness due to a shift in pH value cannot be excluded. Exceptions are homeopathic drugs with potencies of D6 and higher.

Interactions with other drugs are not known

- In a phase I study it was demonstrated for Helixor® A that the pharmacokinetics of the cytostatic gemcitabine were not affected.[87]

- In general, Helixor® A, M and P showed no effect on the liver metabolism via inhibition or induction of cyto-chrome P450 isoenzymes.[7, 168]

- Based on widespread clinical use and knowledge of the pharmacological effects, there were no indications for interactions with oncological products such as cytostatics, targeted therapies antibodies, kinase inhibitors, etc.) or antihormonal substances.

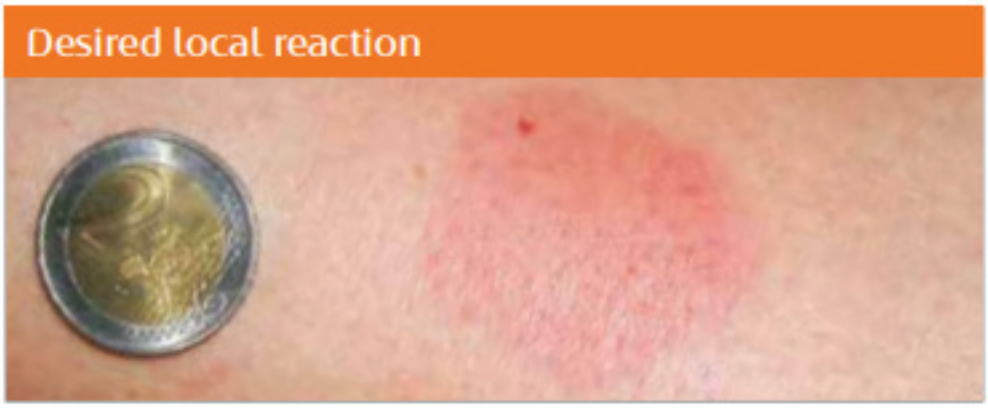
Control Parameters for the Patient's Response to Mistletoe Therapy

The following criteria are based on the previously described mode of action of Helixor® and have proven their value for therapeutic monitoring in practice.

Local Reaction

The local reaction at the subcutaneous injection site is the main criterion for the individual procedure during induction therapy. This is harmless and desired[81] as it demonstrates that the skin's immune cells have been activated by the administered dose.

This presents as localized reddening, hyperthermia, swelling and induration (caused by the accumulation of macrophages and lymphocytes), and is occasionally accompanied by localized pruritus or mild pain. It reaches its maximum size after 2 – 3 days, and then regresses completely within a few days and only occasionally persists for one to two weeks.



Local Reaction (cont.)

The local reaction is best checked immediately prior to the next planned injection.

- For local reactions up to a diameter of 5 cm, the dose of Helixor® should not be increased further and should be reduced by one dose level in case of borderline reactions.
- If the local reaction exceeds a diameter of 5 cm or if the patient is affected by pain or pruritus, then a significant dose reduction of two dose levels is recommended (see page 35).
- In addition, one should wait to administer the next injection until the existing local reaction has subsided. If these precautionary measures are not observed, the local reactions may become extensive and in rare cases can lead to local or extensive blister formation.

The degree of local inflammatory reactions can be well controlled by reduction of the dose. As a rule, the tendency to develop such reactions diminishes over time and finally disappears altogether due to the ncreasing titer of anti- mistletoe antibodies.

Temperature Reaction

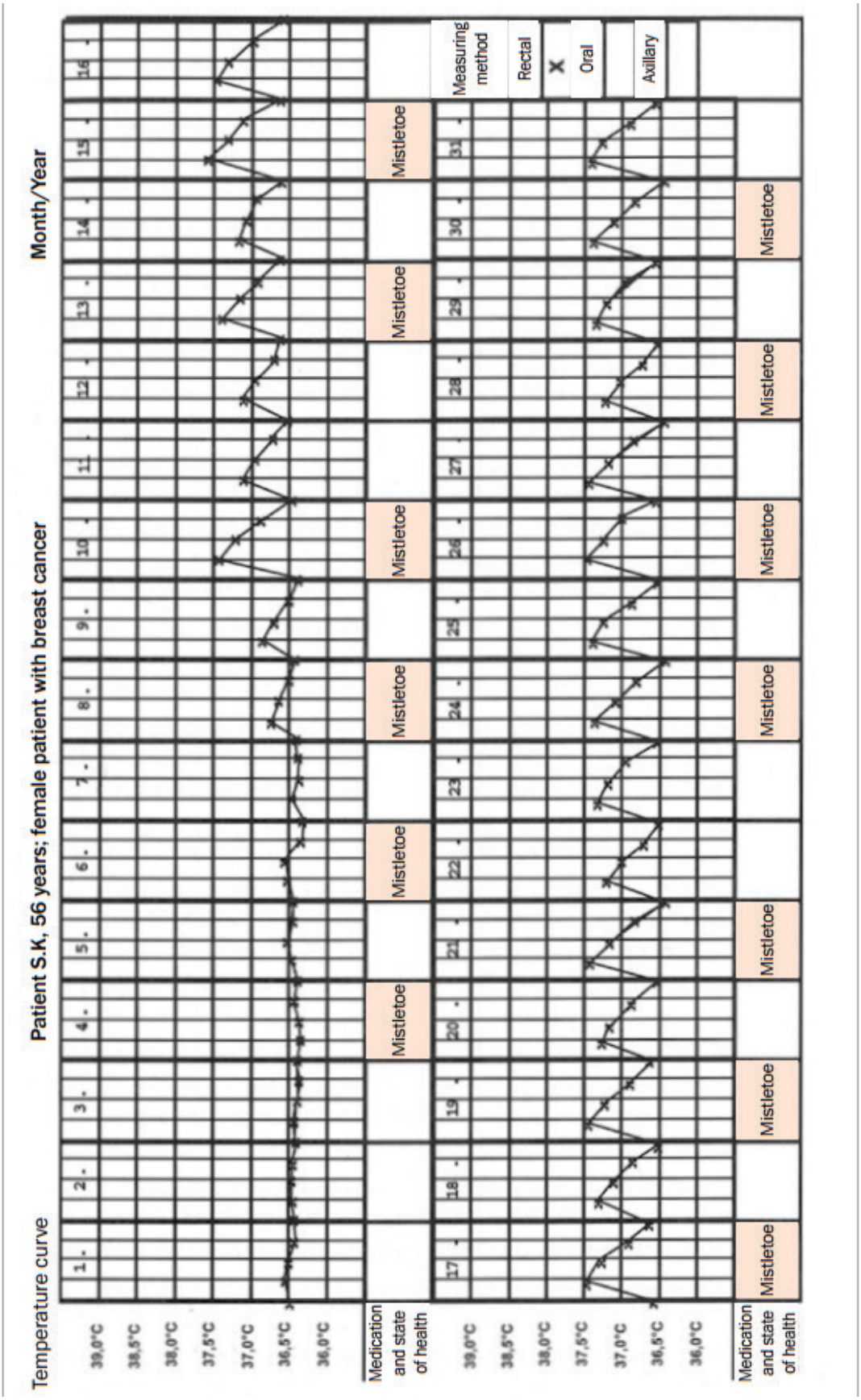
During the first few weeks of mistletoe therapy, the following phenomena can be observed as signs of response, either alone or in combination. They are mainly caused by the release of proinflammatory cytokines:

- Elevated temperature (between 0.5 – 1 °C ^= 0.9 – 1.8 °F, rarely fever) 4 – 12 hours following injection. This often leads to a feeling of warmth instead of feeling cold and shivering.
- A rise in mean temperature level, which is often very low in tumor patients.
- Increase in temperature amplitude by at least 0.5 °C ^ 0.9 °F, also on injection-free days. As a result, the flat or chaotic temperature curve which is typical for tumor patients regains a pronounced daily rhythm.

To generate temperature curves, the patient's temperature is measured orally, or even better, rectally, for two days at two-hour intervals, ideally with the patient at rest.*

On the following days, this is limited to measurement in the morning before getting up and a further measurement at the point of expected temperature maximum. Precision is increased by a half-hour break beforehand. During maintenance therapy, temperature measurement is recommended sporadically only for check-up purposes (e.g. every 3 months for approximately 1 week).

Temperature Reaction to Subcutaneous Mistletoe Injections



56-year old female patient with breast cancer and circadian temperature rigidity. Mistletoe injections (Helixor® M) given 3x per week led to a pronounced circadian temperature rhythm with temperature differences of 1°C.

Source: Matthes, H.: in Scheer, R. et al. (Hrsg.) Mistletoe in tumor therapy, Basic Research and Clinic, KVC-Verlag Essen 2001, 253 - 274.

Improvement of General Condition and Quality of Life

Typical effects include:

- Increasing performance and zest for life
- Reduction of cancer-related fatigue
- Normalization of body rhythms (temperature, sleep, digestion)
- Increased appetite
- Improvement of nausea/vomiting
- Emotional well-being
- Improvement of depression and anxiety
- Decrease in tumor-related pain

In some patients, improvement begins already during the first few weeks of therapy. Specifically an inner feeling of warmth occurs fairly soon. In case of pronounced complaints, it often takes several months until a significant improvement in quality of life occurs. In a study with Helixor® long-term therapy in breast cancer, it was shown that the benefit in terms of quality of life increased consistently over a period of five years compared with the untreated control group, which confirms the value of long-term therapy with mistletoe products.

Laboratory Parameters

Blood count with differential blood count

- Initial: leukocytosis with a left shift
- From week 3: dose-dependent increase in eosinophils (usually to 5 - 10%, rarely 10 - 50%)
- After 1 - 3 months: increase in absolute lymphocyte count (desired: 1,300 - 3,000)

Monthly check-up during the induction phase, later every three to six months.

The value of the relatively expensive determination of the lymphocyte subpopulations is subject to controversy. As a rule, determination of the absolute lymphocyte count is sufficient, as therapy with Helixor® typically leads to an increase in all subpopulations, with a significant preference for T helper cells versus the T suppressor cells, so that the quotient T4/T8 also increases.[21, 25, 29] Of far greater significance for tumor behavior are the immunological conditions in the microenvironment of the tumor, which are so far not available in vivo during examination of the patients.

For reasons of safety, extensive immune controls including lymphocyte subpopulations are recommended only when combining with other immunomodulators such as thymus preparations.

As a rule, advanced, progressive tumors are accompanied by localized and systemic chronic inflammatory changes, which present themselves as accelerated blood sedimentation rate and increased acute-phase proteins such as CRP. Successful mistletoe therapy leads to a significant reduction of these inflammatory changes which are manifested as a tendency towards normal for ESR and CRP. Therefore, the monitoring of these inflammation parameters is of importance for advanced metastasizing tumors.

Regression or Stagnation of Tumor Progression

As a rule, subcutaneous mistletoe therapy does not lead to tumor regression. However, it can lead to retardation or stagnation of tumor progression. However, if mistletoe therapy should lead to tumor regression, this usually takes a longer period of approximately six months when compared with chemotherapy. Therefore as a rule, a combination with oncological treatment is necessary to achieve a rapid tumor response.

Practical Principles for Administration

Selection of Type: Helixor ® A, Helixor ® M, Helixor ® P

Individual, depending on disease and therapeutic goal

Method of Administration

Subcutaneous as a rule

Injection Frequency and Pauses

2 - 3 times per week

Duration of Administration

Patient-oriented

Dosage

Patient-oriented

- ### Individual Dose Modification

  Recommendation for every situation

- ### Dose Adjustment During Chemotherapy or Radiotherapy

  Take into account a change in the reaction

Measures in Case of Excessive Reactions

A pause is always good

Desensitizing Therapy

Tolerability through finely adjusted, small dose steps

Selection of Type

Differences between Helixor ® A, Helixor ® M, and Helixor ® P

The choice of product allows “fine-tuning” of mistletoe therapy for the individual situation of the patient. The following Helixor ® types are produced from the three different subspecies of the white-berry mistletoe:

Helixor® A (Abietis) made from fir mistletoe

Helixor® M (Mali) made from apple tree mistletoe

Helixor® P (Pini) made from pine mistletoe

Differences between Helixor ® A, Helixor ® M, and Helixor ® P (cont.)

Besides botanic characteristics, the following differences between the individual types are known:

- A differing qualitative and quantitative material composition from which different patient reactions can be expected. Hence, a change in Helixor® types is often successful in case of intolerability or insufficient or weakening effectiveness (see page 27).

- Empirically-documented and scientifically-confirmed differences with regard to the tumor-inhibiting, immunostimulating and protective effects.

  → Helixor® A, followed by Helixor® P, has the most pronounced immunoprotective and invigorating effect.
  → Helixor® P, followed by Helixor® M and Helixor® A has the most pronounced tumor inhibition and stimulation of acute inflammatory reactions (local reaction, fever). This ranking correlates with the mistletoe lectin content of the Helixor® products.

- Add to this the aspects resulting from the anthroposophic knowledge of man and nature and the decades of proven clinical administration: The same way in which a tumor relies on the body, the mistletoe needs the tree as a basis of life. Whereas the effect of the white-berry mistletoe is directed at the tumor, the host tree as mistletoe carrier represents the relationship between the organism and the tumor carrier. This results in relationships between the mistletoe tree on the one hand and the constitution of the patient and the organ localization of the disease on the other.

Constitutional Aspects

- **Fir mistletoe** best matches the nervous-sensitive type of patient (more likely to be slim, low fat storage; synonyms: asthenic/leptosomic constitution according to Kretschmer or ectomorphic somatotype according to Sheldon).
- **Apple tree mistletoe** best matches the metabolic type (more likely to be of stocky body build, obese; synonyms: pyknic constitution according to Kretschmer or endomorphic somatotype according to Sheldon).
- **Pine mistletoe** holds an intermediate position (synonym: athletic constitution according to Kretschmer or mesomorphic somatotype according to Sheldon).

Organ Localization of the Disease

- **Fir mistletoe**, e.g. for tumors in the head, neck and lung regions as well as prostate cancer.
- **Apple tree mistletoe**, e.g. for tumors in the stomach and abdomen
- **Pine mistletoe**, e.g. for tumors of the skin, connective tissue, the lymphatic system as well as retroperitoneal tumors of the stomach

Helixor® - Selecting and Changing Types

Question 1 – Patient details

Is at least one of the following situations present:
sensitive patient, allergy, planned or ongoing chemotherapy
or radiotherapy or reduced general condition?

Yes

No

Continue with question 2

Question 2 – Type of tumor

Which type of tumor is present (see also table on page 106)?

- Head and neck cancer
- Lung cancer
- Prostate cancer

- Breast cancer obese/ postmenopausal
- Bladder cancer
- Gynecological or gastrointestinal cancer

- Breast cancer slim/ premenopausal
- Sarcoma
- Skin cancer
- Kidney cancer
- Testicular cancer

Question 3 – Change of type

Is chemotherapy or radiotherapy completed, is the patient's reaction insufficient,
or are there repeated excessive local reactions?
Please check if a change of type is needed (see page 37).

Procedure for the Selection of Type

1. First it needs to be clarified whether one of the following situations is present where Helixor® A should be primarily used:

- Ongoing chemotherapy or radiotherapy
- Known allergy/atopy
- Secondary autoimmune disease (Do not administer in case of florid disease!)
- Excessive local reactions to other mistletoe products
- Reduced general condition, well advanced tumor stage, tumor fever, cachexia

2. Differentiate the selection of types depending on the type of tumor:

Helixor® A

- Head and neck cancer, e.g. ENT cancer, thyroid cancer, brain tumors and metastases
- Lung cancer
- Leukemias (other than CLL) and plasmacytoma
- Prostate cancer

Helixor® B

- Breast cancer (see also obese type and postmenopausal)
- Gynecological cancer (ovary, uterus)
- Gastrointestinal cancer (e.g. stomach, intestine, liver, pancreas)
- Bladder cancer

Helixor® P

- Breast cancer (see also athletic to slim type and premenopausal; in pronounced asthenia choose Helixor ® A)
- Skin cancer, e.g. malignant melanoma, basal cell carcinoma, squamous cell carcinoma
- Testicular cancer (seminoma, embryonal carcinoma)
- Kidney cancer
- Sarcomas
- Neoplasias of the lymphatic system, e.g. chronic lymphatic leukemia (CLL), Hodgkin's lymphoma and non-Hodgkin's lymphoma, thymoma
- Carcinomas with multiple or diffuse metastasis

The product recommendations proven in practice for various tumors are found in the table on the last pages (see page 77).

Alternatively, a selection of types according to constitution may also be considered (see page 25), especially when the tumor-inhibiting effect is not the focus.

Indications for a Change of Type

A change in the type of Helixor® is advisable in the following change-of-type cases:

- Consistent tendency towards excessive local reactions: Change to Helixor® A (see also page 52)
- Insufficient patient reaction or suspicion of decreasing effectiveness under long-term therapy: Helixor® A → Helixor® M → Helixor® P
- After completion of chemotherapy or radiotherapy: change from Helixor® A to M or P if none of the recommendations for Helixor® A apply and more pronounced immunostimulation is desired.

Method of Administration

Guidelines for Subcutaneous Injection

- Do not inject near inflamed skin areas, areas intended for surgery or fresh surgical scars: Always avoid areas treated with radiotherapy.

- Due to the frequency of local inflammatory reactions it is necessary to always inject at varying sites (abdominal wall, thigh top front), in particular during induction therapy. The local reaction at the last injection site must have subsided before administering the next injection.

- During maintenance therapy it is recommended to administer the injection near the (former) primary tumor (e.g. injection into the corresponding head zone in the case of pancreatic carcinoma). Here too, injections should always be administered at varying sites.

- Exception: Avoid the sites of surgery in breast cancer!

- In the case of still present tumors, injecting as near as possible to the tumors (e.g. peritumoral or intratumoral injection) is the most effective.*

- Initially the injections should be administered in the clinic or by a professional and the reactions monitored (see page 17). After receiving appropriate instructions, the patient or a relative can administer the injections. In this case, one should select the abdomen or the thigh as the injection site.

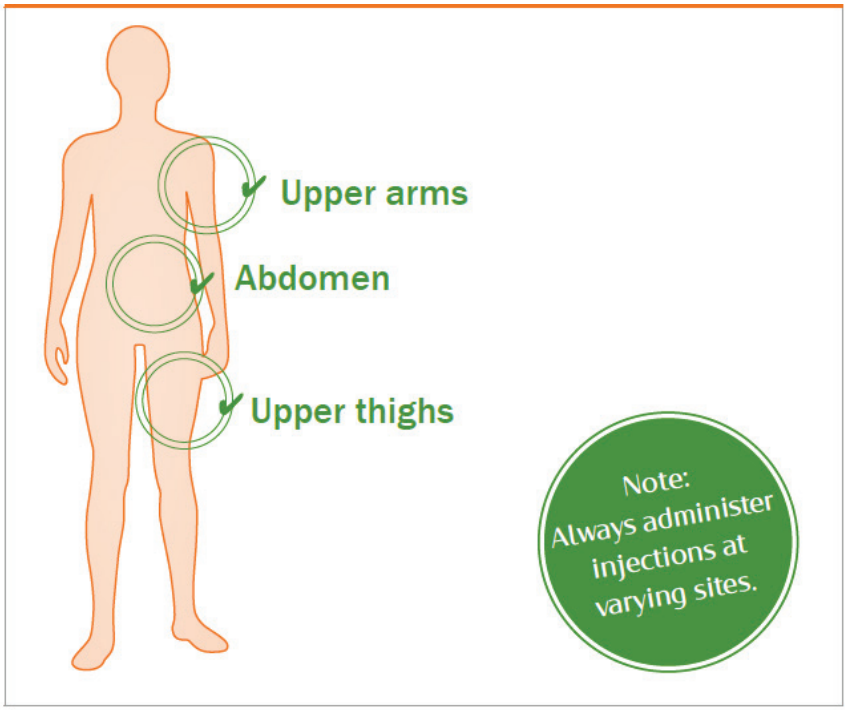
Injection Technique

Do not inject too deep or too superficially.
The injection is ideally inserted into the middle of the subcutis of the skin (injection with a short needle at an angle of approximately 45°, after forming a 2 – 3 cm thick fold of the skin).

- Injections into the deep subcutaneous fatty tissue are prone to form tough nodules which can persist for a relatively long period.

- The more superficially the injection is administered, the more pronounced the local inflammatory reaction will be. This will be the most with strictly intracutaneous injection.

Preferred Injection Sites



Injection Frequency and Pauses

Injection Frequency	
Adjuvant therapy (relapse prevention)	Palliative therapy
In the first two years post-surgery: **3x per week** From the third year post-surgery: **2x per week**	3x per week
Exception: combination with other immunomodulators: **2x per week**	**Exception**: poor general condition or rapid progression: **daily**

Therapy Pauses (only during maintenance therapy)	
Adjuvant therapy (relapse prevention)	Palliative therapy
2 weeks pause after 2 SE or 4 weeks of therapy	No breaks
Exception: during chemotherapy or radiotherapy, suspected relapse: **no pauses**	**Exception**: remission lasting at least 3 months: **1-2 weeks pause** after 4 weeks of therapy

Modulation of Injection Frequency

In individual cases, the injection pauses can be varied on the following basis:

- The regular frequent administration of constant stimuli leads to a gradual weakening of the reaction.
- In contrast, occasional, small stimuli at intervals are stimulating. This effect can be reinforced if the stimulus is always given during the phase of physiologically increased reaction responsiveness.

As mistletoe therapy is a type of stimulant and regulation therapy, the following guidelines can be arrived at:

From experience, stronger reactions can be achieved by:

- Administering injections 2 or 3 times per week, thus allowing the body sufficient time for a reaction
- Rapid dose increase
- Regular pauses, e.g. 2 weeks pause after 4 weeks of therapy
- Rhythmic dosing with periodically recurring increasing doses instead of a constant linear dose
- Adaptation to the circadian rhythm through injections in the morning or early mid-morning during the beginning ergotropic phase
- Adaptation to the circaseptan and circadecan rhythm with injections on day one, two and five of each week. According to the studies to date, this allows stronger temperature and immune reactions to be obtained than with daily injections or every two days.

Modulation of Injection Frequency (cont.)

This procedure is indicated in hyporeactive patients in good general condition where a pronounced stimulation of inflammatory immunological and regulatory processes is desired.

Weaker reactions result from:

- Daily Injection
- Slower dose increase (e.g. by using OP instead of SE, possibly introducing intermediate dose steps)
- Avoiding pauses
- Maintenance therapy with consistent dose

This procedure is indicated for:

- Tumor patients at a very advanced stage of the disease and with a reduced general condition, where a powerful stimulation of the defense mechanisms is no longer reasonable and where rest and pain relief have absolute priority.
- Tumor fever, which often responds to this treatment. However, doses higher than 50 mg should be avoided.
- Patients prone to allergy, atopia, autoimmune diseases or excessive local reactions.
- Malignant systemic diseases (malignant lymphomas, plasmacytomas, leukemias), which already tend towards febrile and inflammatory reactions (e.g. B-symptoms of malignant lymphomas).

Note: Deciduous tree mistletoe products (Helixor® M) are to be avoided in all these cases, instead using coniferous mistletoe products (Helixor® A, also Helixor® P in malignant lymphomas).

In most patients with advanced disease, it is recommended to strike a balance between stimulation and rest by administering injections 3x weekly (Monday, Wednesday, Friday) up to daily injections in rhythmic dosage. If a patient feels considerably worse on injection-free days or during pauses than on the days of injection, then this is an indication that one should change to daily injections without a pause.

While intravenous, intralesional, intrapleural, nasal, and intraperitoneal applications are reported in countries where this is approved, it is not recommended to attempt such procedures without advanced clinical training, supervision, and the appropriate clinical setting capable of providing emergency care for all possible adverse outcomes.

Duration of Administration

As a matter of principle the treating physician decides on the duration of treatment.
Therapy for the prevention of relapse following surgery should be carried out as long as increased risk of relapse exists.

- As a rule, a two-year intensive therapy and subsequent gradual phasing out with increasingly longer pauses can be recommended. In general, mistletoe therapy can be discontinued after 5 years.

- In case of risk factors, especially with tumors tending towards late relapses (e.g. breast cancer, renal cell carcinoma, malignant melanoma), the prevention of relapse should not be discontinued after the 5th year and should be continued as long-term treatment (e.g. 2 SE 2x per year).

PROPHYLAXIS
Selection of type: see pages 23 and 77

Injections: at varying sites of the abdomen, upper thighs or upper arms

TREATMENT SCHEDULE
2 cures per year of 14 injections each
Stage I: 1 SE I ▶1 SE II
Stage II: 1 SE III ▶1 SE IV
Stage III: 1 SE IV ▶1 SE IV + 50 mg combined

If a relapse is suspected or in case of high physical or emotional stress, in particular fatigue, depression, or sleep disturbances, it is recommended to temporarily intensify relapse prevention until the complaints have improved significatnly. See page 43.

Therapy Pauses: none during the cures

Selection of type: no restrictions

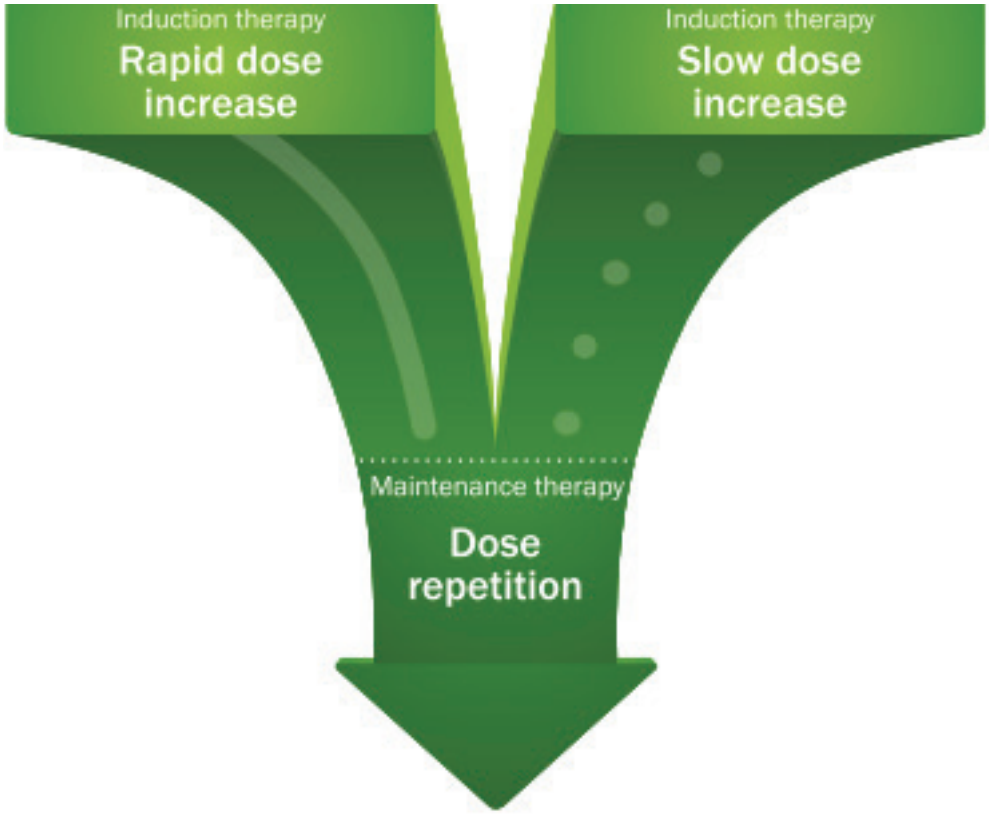
- In stressful life situations which from experience are associated with an increased risk of relapse (major accidents and surgery, emotional stress), the prevention of relapse should be reinstated or intensified. This also applies to fatigue conditions, sleep disturbances, depression, conditions after serious viral infections, an increase in infections, as well as a sudden and persisting worsening of the immune status.

The palliative therapy of inoperable or metastasizing tumors and incurable systemic diseases should be continued indefinitely as long as the patient benefits.

As with every oncological treatment, the indication for Helixor® needs to be reexamined in lack of therapeutic success (no improvement or stabilization of the general condition). Improvement may still be achieved in many cases by changing the product, dose modulation, other modes of administration or combination with other therapies.*

Dosage

Mistletoe therapy with Helixor® proceeds in two phases which differ entirely in their dosage: induction therapy and maintenance therapy. Induction therapy can be carried out with rapid or slow dose increase.



Induction Therapy

Induction therapy consists of stepwise dose increase, starting with the 1 mg dose, until the individual optimal dose (individual reaction dose) or the maintenance dose recommended in the treatment schedule is reached.

Such a stepwise dose escalation until the desired clinical effect is achieved is also common to numerous other drugs, for example, in pain therapy with opioids, in antihypertensive therapy or antimycotic therapy with amphotericin B. Stepwise dose increase during induction therapy recommends itself for the following reasons:

- It allows individual dose optimization.
- It allows for good tolerability.
- It has proven itself in administration over decades.
- Its efficacy has been investigated in more than 20 clinical studies with Helixor®.

Induction Therapy (cont.)

If therapy begins directly with a dose of more than 1 mg or if the dose is increased too rapidly, this can result in severe, extensive inflammatory reactions as well as fever and flu-like symptoms (see page 25).

- The series packs (SE) are available for rapid dose increase and contain 7 ampoules with increasing doses.
- If a slower dose increase is indicated, the original packs (OP) with 8 ampoules each of the same dose are available.
- During the induction phase one must allow for an increase in inflammatory reactions from injection to injection. Therefore it is necessary to check the patient's reaction to the preceding injection prior to the next injection (local reaction at the SC injection site, temperature, general well-being).
- The next injection may only be administered after the inflammatory reaction has disappeared completely, regardless of the injection intervals recommended in the treatment schedule.
- The patient may only receive the next higher dose if the previously administered dose did not cause any inflammatory reactions, regardless of the dose escalation recommended in the treatment schedules (see page 17).

Maintenance Therapy

Induction therapy is completed once the dose recommended in the treatment schedule has been reached or if the patient shows a clear, persistent reaction to a lower dose of Helixor®. In this case the dose should not be increased further for the time being. In fact, the reaction dose should be maintained as the maximum dose in a rhythmic sequence with lower doses.

Only when there are no more reactions to the injection of Helixor® should the dose be increased according to the Helixor® treatment schedule.

The constant change between higher and lower doses is to avoid tolerance during maintenance therapy and the patient reaction can therefore be maintained over a longer period of time.

Individual Dose Modification

Maintain the most recent dose

Even if a higher dose is recommended in the treatment schedule, the dose should not be increased further in case of subsequent reactions (see also "Control parameters for the patient's response to mistletoe therapy", page 17).

This **individual reaction dose** is maintained until none of the above mentioned desired reactions occur. Then the dose should be increased again until a desired reaction occurs or until the maintenance dose given in the Helixor® treatment schedule is reached.

Individual Dose Modification (cont.)

Dose Reduction

This is indicated in the following cases:

- Excessive local reaction at the SC injection site (diameter greater than 5 cm and/or severe pruritus or pain, possibly blister formation)
- Regularly elevated temperature over 38 °C (=^ 100.4 °F) following injection
- Fatigue lasting over 24 hours, possibly in combination with head and limb pain, dizziness and a feeling of flu

Dose Increase During Maintenance Therapy

This is indicated in the following cases:

- If initially severe inflammatory reactions, which led to a relatively low maintenance dose, subside during the further course and do not reoccur. àstepwise dose increase according to the treatment schedule up to the recommended maintenance dose or renewed occurrence of a marked individual reaction.
- In case of a suspected relapse (e.g. continuous increase of tumor markers) àstepwise dose increase according to the treatment schedule for stage IV (inoperable or metastasizing tumors, see page 45).
- If there is no satisfactory therapeutic outcome in inoperable or metastasizing tumors (no improvement of quality of life, no inhibition of tumor growth) àstepwise increase in maintenance dose by 50 mg each time, possibly changing to daily injections. Maximum dose: 400 mg daily SC

Recommendation Following Prolonged Therapy Pause

If therapy is continued at the last administered dose after a therapy-free interval of more than four weeks, this can lead to possible excessive reactions. It is therefore recommended to initially reduce the dose by half after a prolonged pause in therapy. In the case of series packs, this is achieved by renewed use of the same series pack.

Dose Adjustment During Chemotherapy or Radiotherapy

Chemotherapy or radiotherapy are not a reason for discon- tinuing or interrupting treatment with Helixor® A. In fact, a combination of Helixor® A with these therapies is advisable to increase their tolerability as far as possible. However, one should carefully consider whether the Helixor® dose given so far needs to be for a patient undergoing chemotherapy or radiotherapy.

Therapy pauses are not recommended as continuous therapy is necessary for better tolerability of oncological therapies.

Dose Adjustment During Chemotherapy or Radiotherapy (cont.)

Chemotherapy

Even when using Helixor® A, previously well-tolerated doses can lead to excessive reactions during chemotherapy (local reactions, fever, allergic reactions). The reason could be a blockade or excessive demands on the compensation and regulation reserves of the body, in concrete terms for example, a reduced production of anti-mistletoe antibodies as chemotherapy may also reduce β-lymphocytes. For this reason, close monitoring of the patient reaction and if required a dose reduction are recommended.

Radiotherapy

During radiotherapy and the following weeks (maybe even months), there is a tendency of inflammatory reactions to radiotherapy damage to occur in form of radiotherapy dermatitis, mucositis, enteritis etc. (depending on the irradiated area). During this phase of an increased disposition to inflammation, the patient may react more sensitively to Helixor® thus often requiring a dose reduction.

This is followed by a second and longer phase, where atrophic degenerative processes, immunosuppression and a reduced tendency toward inflammation prevail. An increase in the dose of Helixor® is often indicated in this phase.

Measures in Case of Excessive Reactions

Definition

- Excessive local reaction: skin reactions around the injection site > 5 cm diameter (possibly with pronounced pruritus or pain)
- Excessive temperature reaction: elevated temperature > 38 °C (=^ 100.4 °F)
- Occurrence of flu-like symptoms

Measures to be taken stepwise:

STEP 1: Pause in therapy until subsided: If possible, do not treat localized inflammation and fever antiphlogistically or antipyretically. Wet compresses or ointment dressings can provide local relief (e.g. Calcea wound/healing cream).

STEP 2: Dose reduction: After the reaction has subsided, therapy should be continued at a significantly reduced dose, whereby the last given dose is reduced by two dose levels (e.g. from 10 mg to 1 mg, from 5 mg to 0.1 mg*). In case of fever, it is sufficient to reduce the dose by one dose level.

STEP 3: If well tolerated: Seven further injections with this dose (one OP)

STEP 4: Dose Increase: If reaction disappears completely, renewed dose increase in small steps.

Measures in Case of Excessive Reactions : Definition (cont.)

- If the tendency to inflammation persists despite a therapy pause and dose reduction, or if excessive local reactions continue to occur during dose increase, then a change to a different type of Helixor®, preferably Helixor® A, is indicated.

- In rare cases when even Helixor® A is not tolerated, we recommend injection treatment with our Helleborus products as an alternative, but only in palliative therapy situations. These products, made from Helleborus niger (Christmas rose) and Helleborus foetidus (bear's foot), are manufactured in the same way as Helixor®. They display similar cell growth inhibiting effects, but no inflammation stimulating or allergenic effects. This is why they are taken into consideration particularly for tumor patients with pronounced inflammatory symptoms or a tendency towards allergies.*

Desensitizing Therapy

Definition: This does not mean hyposensitization for the treatment of allergies, but a process for reducing reactions through repeated small stimuli using Helixor® dilutions 0.01 and 0.1 mg.**

Indications

- Tumor patients with concomitant autoimmune disease or pronounced allergic tendencies. (Caution: Not in the case of florid autoimmune diseases and those under immunosuppressive therapy!)

- Persistant excessive local reactions or enhanced tumor fever despite dose reduction and change to Helixor® A.

- Some patients display persistant and excessive reactions even at a low dose. This low dose should then be used for maintenance therapy. Therapeutic effectiveness is achieved not necessarily by giving a higher dose, but by using the dose to which the patient responds.

Desensitization

Selection of Type: Helixor® A

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday) one injection strictly subcutaneously
- In disease progression and increasingly reduced general condition: daily injection
- Injection site: continuously varying sites in irritation-free areas

Treatment Schedule

Prior to desensitizing therapy, a pause should be maintained until all acute inflammatory or allergic symptoms have disappeared.

Induction Therapy:

- 8 injections 0.01 mg (1 OP 0.01 mg)
- Followed by 4 injections 0.05 mg (0.5 ml from 1 ampoule or ½ ampoule 0.1 mg*)
- Followed by 4 injections 0.1 mg (1 OP 0.1 mg)
- Followed by 4 injections 0.5 mg (0.5 ml from 1 ampoule or ½ ampoule 1 mg*)
- Followed by 4 injections 1 mg (1 OP 1 mg)
- Followed by 4 injections 2.5 mg (0.5 ml from 1 ampoule or ½ ampoule 5 mg*)
- Followed by 4 injections 5 mg (1 OP 5 mg)
- Followed by 4 injections 7.5 mg (0.75 ml from 1 ampoule or ¾ ampoule 10 mg*)
- Followed by 4 injections 10 mg (1 OP 10 mg)

**Note:* *Please discard the rest of the opened ampoule.*

Desensitization

Continuation of Therapy: If the dose of 10 mg is well-tolerated, the dose can be further increased according to the usual slow treatment schedule (see page 41) depending on individual reactions and the tumor stage.

Therapy Pauses: None in case of good tolerability.

Duration of Therapy: Approximately 13 weeks until change to the usual slow treatment schedule.

Therapy Regimens

Therapeutic Principles

Individual therapy, adjusted to individual patients

Solid Tumors

Take tumor stage and therapeutic situation into account

- Relapse Prevention Following Curative Therapy
- Duration of Relapse Prevention
- Preoperative Therapy
- Procedure in Case of Relapse
- Palliative Therapy of Inoperable and/or Metastasizing Tumors

Special Features of the Most Common Solid Tumors

Therapy regimens for individual types of tumors

- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Prostate Cancer

Therapy for Special Types of Tumors

Note on special cases

- Brain Tumors and Brain Metastases
- Sarcomas
- Malignant Systemic Diseases
- Defined Precancerous Conditions

Therapeutic Principles

The following special treatment schedules and recommendations are based on many years of clinical experience with Helixor® and have proven themselves in practice. However, they should be varied individually depending on the general condition and reaction of the patient (see page 17).

Fundamentally, mistletoe represents a therapy which is indicated in all types of tumors. This can be explained in that the effect of mistletoe is not directed specifically at the tumor in a cytostatic manner, but affects the entire organism and stimulates the body's growth regulation, differentiation and immune response capabilities. Mistletoe therapy is to be adjusted to the different host-tumor relationships of the various types of tumors through the differentiated use of the various types of mistletoe (Helixor® A, M and P, see page 23).

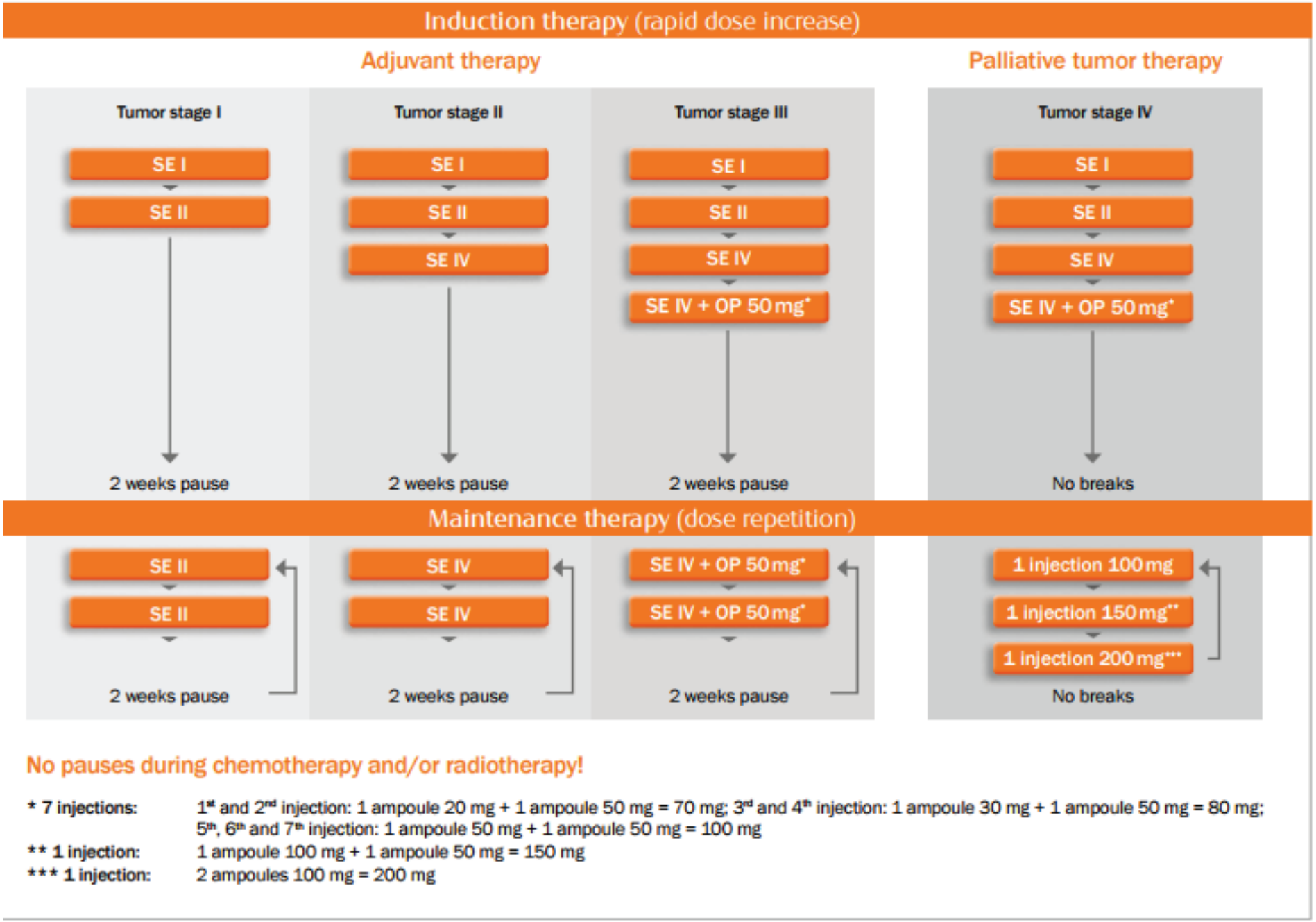
Tumor-inhibiting effects are most likely to be observed for carcinomas (mainly in elderly persons) and maybe also in high-dose and tumor-proximal administration. These effects are less likely however in sarcomas, malignant systemic diseases and primary brain tumors. A high percentage of improvement in general condition, tolerability of chemotherapy or radiotherapy and disposition to infections can be expected for all types of tumors.

Solid Tumors

Experience has shown that higher doses are necessary to trigger a reaction, the more the disease has progressed. A higher degree of malignancy can be viewed as an indication of the reduced ability of the body to form and differentiate tissue. This is why the dose of Helixor® in the following treatment schedules is classified according to the stage of the disease and partly also the degree of malignancy of the tumors.

The stages are classified according to the Union Internationale Contre le Cancer (UICC) – as is customary at an international level. Here, the TNM categories are summarized to five standard prognostic stages for every type of tumor. Exact details are given in the current edition of the TNM classification of malignant tumors (Wittekind Ch and Meyer HJ. TNM: Classification of malignant tumors. Wiley-VCH Publishers).

Tumor Stages : Classical Stage Classification of Carcinomas	
Stage 0	Preinvasive carcinoma (carcinoma in situ)
Stage I	Early local infiltration, no metastases
Stage II	Limited local spreading of the tumor and/or minimal involvement of regional lymph nodes
Stage III	Extensive local spreading of the tumor and/or extensive involvement of regional lymph nodes
Stage IV	Locally advanced tumors or every condition with distant metastases without consideration of local spreading



No pauses during chemotherapy and/or radiotherapy!

*** 7 injections:** 1st and 2nd injection: 1 ampoule 20 mg + 1 ampoule 50 mg = 70 mg; 3rd and 4th injection: 1 ampoule 30 mg + 1 ampoule 50 mg = 80 mg; 5th, 6th and 7th injection: 1 ampoule 50 mg + 1 ampoule 50 mg = 100 mg

**** 1 injection:** 1 ampoule 100 mg + 1 ampoule 50 mg = 150 mg

***** 1 injection:** 2 ampoules 100 mg = 200 mg

Induction therapy (slow dose increase, e.g. during chemotherapy)

Adjuvant therapy

Tumor stage I

- OP 1 mg
- OP 5 mg
- OP 10 mg
- OP 20 mg
- OP 30 mg

2 weeks pause

Tumor stage II

- OP 1 mg
- OP 5 mg
- OP 10 mg
- OP 20 mg
- OP 30 mg
- OP 50 mg

2 weeks pause

Tumor stage III

- OP 1 mg
- OP 5 mg
- OP 10 mg
- OP 20 mg
- OP 30 mg
- OP 50 mg
- OP 100 mg

2 weeks pause

Palliative tumor therapy

Tumor stage IV

- OP 1 mg
- OP 5 mg
- OP 10 mg
- OP 20 mg
- OP 30 mg
- OP 50 mg
- OP 100 mg

No breaks

Maintenance therapy (dose repetition)

Tumor stage I

- SE II
- SE II

2 weeks pause

Tumor stage II

- SE IV
- SE IV

2 weeks pause

Tumor stage III

- SE IV + OP 50 mg*
- SE IV + OP 50 mg*

2 weeks pause

Tumor stage IV

- 1 injection 100 mg
- 1 injection 150 mg**
- 1 injection 200 mg***

No breaks

No pauses during chemotherapy and/or radiotherapy!

*** 7 injections:** 1st and 2nd injection: 1 ampoule 20 mg + 1 ampoule 50 mg = 70 mg; 3rd and 4th injection: 1 ampoule 30 mg + 1 ampoule 50 mg = 80 mg; 5th, 6th and 7th injection: 1 ampoule 50 mg + 1 ampoule 50 mg = 100 mg

**** 1 injection:** 1 ampoule 100 mg + 1 ampoule 50 mg = 150 mg

***** 1 injection:** 2 ampoules 100 mg = 200 mg

Relapse Prevention Following Curative Therapy

Adjuvant therapy after complete tumor resection, curative chemotherapy or radiotherapy
Surgery and radiotherapy are no doubt effective local measures, however, they cannot prevent the systemic spreading of the disease which is caused by invasive tumor cells circulating in the blood. Chemotherapy acts systemically; however, it is seldom curative in the case of metastasizing solid tumors (exception: testicular cancer, chorionic carcinoma, small cell lung cancer).

Mistletoe therapy with Helixor® as a systemic adjuvant therapy has the objective to prevent relapses and, in particular, metastases, by stimulating the body's defense and regulation processes and to prolong relapse-free survival time.

Administered parallel to chemotherapy or radiotherapy as an adjuvant, Helixor® can improve their tolerability, reduce the myelo- and immunosuppressive effects and increase the tumor-inhibiting effect.

Treatment with Helixor® should therefore be started as early as possible, best preoperatively (see page 43): however, at the latest, postoperatively after completion of wound healing. Chemotherapy and radiotherapy are accompanied by mistletoe therapy. After their completion, mistletoe therapy is continued as long-term relapse prevention (duration of therapy see pages 31 and 43).

PROPHYLAXIS
Selection of type: see pages 23 and 77

Injections: at varying sites of the abdomen, upper thighs or upper arms

TREATMENT SCHEDULE
2 cures per year of 14 injections each
Stage I: 1 SE I ▶1 SE II
Stage II: 1 SE III ▶1 SE IV
Stage III: 1 SE IV ▶1 SE IV + 50 mg combined

If a relapse is suspected or in case of high physical or emotional stress, in particular fatigue, depression, or sleep disturbances, it is recommended to temporarily intensify relapse prevention until the complaints have improved significatnly. See page 43.

Therapy Pauses: none during the cures

Selection of type: no restrictions

Duration of Relapse Prevention

- The duration of adjuvant mistletoe therapy depends on the risk of relapse. This is highest in the first 2 years following curative primary therapy. For this reason, maintenance therapy should be continued intensively during this time period as described above, in parallel with close aftercare monitoring.

- After the 3rd year, gradual reduction of therapy is possible. Generally it is not expedient to reduce the dose as the patient responds less to lower doses. The overall dose should actually be decreased by extending intervals, e.g. employing the following schedule:

Reduction of Therapy	
Third Year	3 weeks pause after 2 SE each or 7 weeks of therapy (10 SE per year at 2x weekly injection)
Fourth Year	4 weeks pause after 2 SE each or 7 weeks of therapy (8 SE per year at 2x weekly injection)
Fifth Year	8 weeks pause after 2 SE each or 7 weeks of therapy (7 SE per year at 2x weekly injection)

- If there are no relapses 5 years after curative primary therapy, then, as a rule, relapse prevention can be discontinued.

- In case of tumors with a tendency to late relapses (breast cancer, renal cell carcinoma, melanoma) and high risk of relapse: during the 6th – 10th year continue to administer prophylactic therapy 2x per year (see page 31).

- If a relapse is suspected or in case of increased risk of relapse (e.g. additional diseases, major accidents, surgery, severe physical and emotional stress), resumption of therapy or intensifying ongoing mistletoe therapy by shortening the intervals and possibly increasing the dose is advisable.

Preoperative Therapy

Every surgery leads not only to transient immunosuppression; mechanical manipulation also leads to numerous tumor cells entering the bloodstream. It therefore appears advisable to begin relapse prevention with Helixor® preoperatively and not postoperatively. By activating nonspecific defense mechanisms this can counteract postoperative infections at the same time.

Preoperative Therapy (cont.)

PREOPERATIVE THERAPY
Selection of type: see pages 23 and 77

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday)
- At varying sites of the abdomen or upper thighs
- **Do not inject into areas intended for surgery or radiotherapy**

TREATMENT SCHEDULE

Induction Therapy:

1x SE I ► 1x SE II ► 1x SE IV

If there is no positive reaction, a further dose increase is recommended:
1 SE IV + 1 OP 50 mg combined
(resulting in 70, 70, 80, 80, 100, 100, 100 mg)

Maintenance Therapy: Continuous repetition of the pack or pack combination which led to a positive reaction. **Last dose 2 days before surgery!**

Therapy Pauses: none

Duration of Therapy: depends on the time for which surgery is scheduled. The preoperative start of mistletoe therapy is still advisable even if the dose of 50 mg can no longer be attained for time reasons.

- The last dose should be administered 2 days prior to surgery
- The preoperative start of mistletoe therapy is still advisable even when only a few injections can be administered for time reasons.
- Therapy can be continued postoperatively without reservations as described on page 60 as long as there are no contraindications such as fever or complications of inflammation.
- If neoadjuvant chemotherapy is performed preoperatively, the use of Helixor® A is recommended with original packs for reasons of better tolerability (see treatment schedule slow dose increase page 41).

Procedure in Case of Relapse

In case of localized relapses, new relapse prevention according to the treatment schedule on page 42 is to be carried out after complete surgical removal. To this purpose we recommend:

- A change of types from deciduous to coniferous mistletoe and vice versa:

  Helixor® M ⟶ Helixor® P

  Helixor® A or P ⟶ Helixor® M

  Exception: *Situations where Helixor® A is recommended as a matter of principle*

- A dose increase along the lines of the treatment schedule for that tumor stage which corresponds to the spreading of the relapse (e.g. breast cancer stage I with axillary relapse: relapse prevention according to the treatment schedule for stage II)

For a relapse with distant metastases a high-dose mistletoe therapy corresponding to the treatment schedule for palliative therapy in stage IV has to be carried out.

Palliative Therapy of Inoperable and/or Metastasizing Tumors

- For inoperable or incompletely resected tumors - Stage IV
- For distant metastases
- In case of suspected metastases (continuous increase of tumor markers)

The most impressive results were achieved in particular with Helixor® at high doses with advanced tumors. Remission of tumors is only achieved in exceptional cases. However, one can often observe a slowing down or stagnation of malignant growth. In the majority of patients quality of life can be improved considerably, which is accompanied by normalizing of appetite and weight, stimulation of the digestive tract and excretion activity, sleep and mood improvement, and relief of tumor pain. Many physicians have had the experience that their patients can live extremely long and in good general condition with their tumor disease with the help of mistletoe therapy. This is supported by the results from the clinical studies with Helixor® to date.

Palliative Therapy of Inoperable and/or Metastasizing Tumors (cont.)

PALLIATIVE THERAPY OF INOPERABLE AND/OR METASTASIZING TUMORS (STAGE IV)

Selection of type: see pages 23 and 77

Injections:

- 3x weekly for patients with a satisfactory general condition
- Daily injection for poor general condition, advanced metastasizing tumors, or rapid progression as well as significant worsening of the patient's condition on injection-free days.

TREATMENT SCHEDULE

Induction Therapy:

1x SE I ► 1x SE II ► 1x SE IV + 1 amp. of 50 mg

i.e. One ampoule of 50 mg is drawn with each ampoule of the SE IV (resulting in: 70 mg, 70 mg, 80 mg, 80 mg, 100 mg, 100 mg, 100 mg).

Maintenance Therapy:

Monday 100 mg ► Wednesday 150 mg ► Friday 200 mg

Or in case of daily injection:

Monday & Tuesday 100 mg ► Wednesday & Thursday 150 mg ► Friday **to** Sunday 200 mg

Alternatively, for example during chemotherapy, a better-tolerated slow dose increase can be given using OP from 1 mg to 100 mg in place of SE (see page 41).

Therapy Pauses:

- Progressive metastasizing tumors: no breaks
- Following resection of metastases, with present absence of tumors: 1-2 weeks pause after 4 weeks of therapy
- For remission lasting over 3 months or growth stagnation: careful attempt with 1-2 weeks pause following every 4 weeks of therapy

Duration of Therapy: depends on the time for which surgery is scheduled. The preoperative start of mistletoe therapy is still advisable even if the dose of 50 mg can no longer be attained for time reasons.

If no therapeutic effect is observed after two months of maintenance therapy, the dose can be further increased stepwise, e.g. by increasing the dose by 100 mg approximately every two weeks:

200/250/300 mg ⟶ 300/350/400 mg

Maximum daily dose: 400 mg SC

An increase in the weekly dose can also be achieved by changing from 3x weekly to a daily injection.

Special Features of the Most Common Solid Tumors

Breast Cancer

The greatest experience with mistletoe therapy exists for the most common cancer in women, breast cancer. For Helixor® alone, there are eight clinical studies on breast cancer treating a total of 1,235 patients with Helixor®.[3, 10, 50, 58, 60, 99, 163, 165, 170]

The effect of mistletoe therapy on survival was investigated in four retrospective studies[10, 58, 60, 163, 165] and one prospective randomized study.[50] Whereas there was no difference for stage I compared with the control group, the benefit of mistletoe therapy increased clearly with the tumor stage. The total cohorts, both in the prospetive study and the latest retrospective study, demonstrated significant advantages for Helixor® compared with control groups without mistletoe therapy.

In a further prospective randomized multi-center study in 68 breast cancer patients treated with aggressive polychemotherapy, the concomitant administration of mistletoe therapy resulted in a significant improvement of quality of life (in specific, pain, fatigue, insomnia, nausea, appetite and physical activity) as well as in a reduction of chemotherapy adverse reactions.[99] A further randomized study in 65 breast cancer patients in stages I – III under polychemotherapy (FAC), showed a significant improvement of quality of life in terms of emotional, cognitive, and social function, nausea and vomiting, pain, insomnia, lack of appetite, constipation and diarrhea under concomitant Helixor® A treatment. Better tolerability of chemotherapy was demonstrated by a lower incidence of neutropenia and a smaller number of delayed chemotherapy cycles in the Helixor® group.[170] Another double-blind randomized pilot study showed that Helixor® A significantly reduced immunosuppression under radiochemotherapy (CMF, sandwich regimen) compared to placebo, in conjunction with a lower rate of leukopenia.[3]

Main indications for mistletoe therapy in breast cancer:

- Adjuvant therapy following complete tumor resection: This not only has relapse prevention as the goal, but also comprehensive salutogenesis after often severe oncological therapeutic interventions, with the restoration of disturbed body rhythms, in particular the sleep-wake cycle, with improvement in fatigue, the inner feeling of warmth, and performance capacity. A pharmacoepidemiological long-term study demonstrated that improvement in quality of life increased year by year under mistletoe therapy, which underlines the relevance of adjuvant long-term therapy over at least five years.[10] This positive effect of mistletoe therapy even had economic benefits: The average total costs for aftercare were not even half as high in the Helixor® group as in the control group.[126]
  Due to the risk of late relapses, it is recommended to conduct two prophylactic therapies per year following this five-year period (best during spring and fall, see page 31).

Breast Cancer (cont.)

- Additive therapy in combination with standard oncological therapy: Better tolerability of chemotherapy (specifically the reduction of fatigue, bone marrow suppression and immunosuppression, as well as nausea and lack of appetite) is particularly well documented in breast cancer through new studies.[3, 10, 99, 170] The positive effects on survival demonstrated in other studies can be explained in that the full dose of chemotherapy can be administered more often under adjunctive Helixor® A therapy and that there are fewer delays in cycles.[83, 170] Experience has shown that radiotherapy is also tolerated better with adjunctive mistletoe therapy. Combination with hormone therapy has also proven very successful. In contrast to chemotherapy and radiotherapy, the immunostimulating effect of Helixor® is not negatively affected by hormone therapy. Adverse reactions such as nausea, vomiting, and fatigue can be reduced with Helixor®, although not the often-irritating hot flushes. The combination with bisphosphonates and new targeted therapies (in particular herceptin) has been well-tried in practice.

- Palliative therapy of metastasizing breast cancer: Especially in palliative therapy, improving quality of life and relieving tumor symptoms (e.g. tumor pain, fatigue) is paramount. In the case of the fairly frequent pleural effusions, the intrapleural instillation* of Helixor® P presents an alternative to talcum pleurodesis with its many adverse reactions or the instillation of cytostatic agents.[77, 157, 158, 166] Intrapericardial instillation* with Helixor® P in malignant pericardial effusions has so far proven effective in every case.[113] Malignant ascites also occurs quite frequently: Here too, intraperitoneal instillation* with Helixor® M can also lead to a significant reduction in ascites formation up to complete remission.[42, 67, 134]

Start of Therapy:

- It is recommended to begin mistletoe therapy as early as possible. In a large epidemiological study it was shown that the survival benefit of mistletoe versus patients not receiving mistletoe therapy was greater the longer consistent treatment was given.*

* *Grossarth-Maticek et al.: Alternative Therapies 2001;7:57-76.*

Breast Cancer (cont.)

Selection of type: Helixor® A in connection with adjuvant chemotherapy/radiotherapy prior to or after surgery. After completion of these therapies and extensive recovery of the patient, a change to the more potent immunostimulating types is advisable:

- Helixor® M for obese/postmenopausal patients
- Helixor® P for slim/premenopausal patients and those with more pronounced menstruation (see page 26). In case of very weak condition, e.g. in well advanced tumors as well as very sensitive and asthenic patients, one should preferably stay with Helixor® A.

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday)
- At varying sites of the abdomen or upper thighs
- Injections in the breast and arm on the operated side should be strictly avoided due to the risk of lymphedema

TREATMENT SCHEDULE
Induction Therapy: see page 40

Maintenance Therapy: see page 40
Most patients with breast cancer are sensitive to Helixor® injections and develop marked reactions even at relatively low doses. Maintenance doses are often not reached, especially in breast cancer. Therefore it is especially important to adjust the dose to the individual reaction.

Therapy Pauses: see page 40

Duration of Therapy: Ideally up to the 5th postoperative year as intensive relapse prevention according to the schedule. As late relapses often occur as late as 10 – 30 years after surgery, it is recommended to administer a prophylactic therapy 2x per year following the 5th postoperative year (see page 31).

Colorectal Cancer

Corresponding to its incidence as the second most common cancer in Germany and the most common in Europe, there is considerable experience with mistletoe therapy in intestinal cancer. The efficacy of Helixor® in this tumor entity was investigated in a total of six clinical studies, treating 1,477 patients overall with Helixor®. Four retrospective studies showed a clear to highly significant prolongation of the median survival time and an increase in survival rate with Helixor® therapy and in a further study a significant drop in relapse rate.[11, 59, 109, 164, 165]

Colorectal Cancer (cont.)

Two prospective studies (one of them randomized) showed that additional Helixor® therapy increased the effect of standard chemotherapy of metastasizing colorectal carcinoma with 5-FU and folinic acid, together with better tolerability (less mucositis and leukopenia).[36, 37] A further publication described the administration of Helixor® as high-dose infusion therapy in 36 patients with advanced colorectal carcinoma. This therapy resulted in good to excellent quality of life in particular, and in many cases exceptionally long survival rates.[107] A case study describes the excellent tolerability of high-dose chemotherapy with 5-FU and concomitant administration of a Helixor® infusion in a 74-year old female patient with metastasized colon carcinoma resulting in objective improvement of her quality of life, documented via EORTC-QLQ-C30, and partial remission.[175] A further case study described the course of a large, inoperable colon conglomerate tumor under combined subcutaneous and intralesional Helixor® M administration over a period of twelve months which led to a virtually constant tumor size and significant demarcation of the tumor, which in the end allowed en-bloc resection. Since the start of therapy, the patient has now lived for three years with surprisingly good quality of life.[112]

Selection of type – ***depending on the therapeutic situation***:

- Adjuvant mistletoe therapy: preferably with Helixor® M, following complete tumor resection to reduce the risk of relapse and to improve the chances of a cure
- Palliative therapy in inoperable or metastasizing cancer: Helixor® M
- In reduced general condition: Helixor® A for subcutaneous injection and possibly also for IV infusion therapy* to improve the quality of life and also to inhibit tumor growth
- Additive therapy: Helixor® A during chemotherapy (in rectal cancer also during radiotherapy) to reduce adverse reactions, particularly in mucositis, nausea, diarrhea, bone marrow and immunosuppression. Here, infusion therapy with Helixor®* appears to be considerably more effective than administration via subcutaneous injection.

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday) · At varying sites of the abdomen

TREATMENT SCHEDULE
Induction Therapy: see page 40

Maintenance Therapy: see page 40
Based on experience, the individual reaction dose in patients with colorectal cancer tends towards the higher dose range.

Therapy Pauses and Duration: see page 40

Useful Concomitant Therapy: Hepatodoron or Vitis comp. 3x 2 tablets daily, bitters to support digestion and intestinal function, e.g. Gentiana lutea D1 3x 20 drops daily. In case of colicky pains Oxalis body compresses (Oxalis folium 20 % 1 tablespoon per ¼ liter of water).

Lung Cancer

Palliative, and in part also adjuvant, mistletoe therapy with Helixor® was investigated in two randomized studies: In one of the two studies in 68 patients with inoperable carcinomas and treated with an aggressive combination of radiochemotherapy, the combination with Helixor® A led to a significant increase in quality of life and a significant decrease in leukopenia and nausea. The somewhat higher remission rate in the Helixor® group was explained by better tolerability of chemotherapy with a lower incidence of therapy drop-outs or necessary dose reductions.[83] In a further multi-center study in 233 patients (including 91 patients with lung cancer), Helixor® A as additive therapy to polychemotherapy led to a significantly improved quality of life which was measured using three independent methods, as well as a distinctive reduction in adverse reactions of chemotherapy.[99]

- The therapeutic goal of mistletoe therapy in lung cancer is predominantly focused on improving general condition and tumor symptoms due to the poor prognosis.

Selection of type: Helixor® A

Helixor® A is particularly indicated in lung cancer due to the usually very pronounced inflammatory and edematous changes in the tumor environment.

In rare cases, where neither palliative radiotherapy nor chemotherapy are conducted and where the patient is still in a good general condition, Helixor® P may also be worth considering due to its stronger tumor-inhibiting effect.

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday)
- At varying sites of the abdomen, upper thighs or upper arms

Treatment Schedule: see page 40

Therapy Pauses and Duration: see page 40

Useful Concomitant Therapy: Experience has shown the combination of Helixor® A with Helleborus niger aquos. or Helleborus foetidus aquos. (Helixor) can provide significantly enhanced effectiveness.

Dyspnea, hemoptysis and mucolysis in particular, can be positively affected by Helleborus. Inhalation with a micro inhaler (D12 à D6 1 – 2x daily) has proven especially wellsuited. However, the subcutaneous injection 3x weekly in daily rotation with the Helixor® injections is also effective.

Prostate Cancer

Mistletoe therapy has also proven useful in medical use for the most common tumor in males. A series of case reports describes the progression of twelve patients with metastasizing prostate cancer under palliative Helixor® therapy: In six of these patients, severe bone pain which had not been allayed by previous conventional therapy was improved significantly with Helixor® treatment. In two of these patients the improvement in quality of life was accompanied by complete remission, and in a further patient the tumor markers decreased. Freedom from pain and tumor remission were also achieved in four further patients, but this success must largely be attributed to concomitant hormone therapy.[172] Other unpublished individual case observations report on a significant PSA drop under palliative Helixor® therapy, in particular with high-dose infusion therapy.* Clinical studies on mistletoe therapy in prostate cancer have, however, not yet been conducted.

Main indications of Helixor® therapy in prostate cancer:

- Neoadjuvant mistletoe therapy in patients under "Active Surveillance": Next to stabilizing the PSA value, the main objective is to improve quality of life through reduction of the often considerable psychological burden, resulting from the fact that only close monitoring is performed and no therapy is provided, despite the diagnosis of cancer.

- Adjuvant therapy following curative surgery, radiotherapy or HIFU** therapy for relapse prevention.

- Palliative therapy in patients with biochemical relapse and "Wait-and-See" strategy: Here we have a similar psychological stress situation as with Active Surveillance following initial diagnosis. The "therapeutic gap" can be closed with Helixor®!

- Palliative therapy in patients that cannot be treated curatively (e.g. "Watchful Waiting") and with metastasizing tumors: The objective is to improve quality of life, in particular fatigue and bone pain, and with Watchful Waiting achieve psychological relief through conducting treatment. If hormone therapy is indicated for the control of symptoms and growth inhibition, the combination with Helixor® as immune therapy has proven itself. Mistletoe therapy can reduce the experienced loss in vitality due to hormone withdrawal but not, however, the associated climacteric symptoms. When hormone therapy fails, Helixor® can provide better tolerability of chemotherapy, e.g. in combination with taxanes.

*** HIFU: highly intensive focused ultrasound*

Prostate Cancer (cont.)

Selection of type: Primarily Helixor® A

Experience also exists for Helixor® M (mainly in cases of metabolic-focused constitution) and Helixor® P, if more potent immunostimulating and tumor-inhibiting effects are desired.

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday)
- At varying sites of the abdomen, upper thighs or upper arms

Treatment Schedule: For relapse prevention following curative therapies see page 42. In case of prostate cancer still being present, use the Helixor® treatment schedule for stage IV (see page 45).

Therapy Pauses and Duration: see page 40

Useful Concomitant Therapy: A combination with Helleborus niger aquos. (Helixor)* at low potencies (D3 – D6) is recommended, especially in patients with Active Surveillance or Watchful Waiting to relieve inflammatory changes in the sense of accompanying prostatitis and to promote diuresis, but also for patients with a weakened general condition and very advanced carcinomas.

Therapy for Special Types of Tumors

Brain Tumors and Brain Metastases

- Helixor® A is worth considering here, both for relapse prevention following complete resection and radiotherapy as well as for the palliative therapy of inoperable or partially resected brain tumors.
- Do not use Helixor® M or P because of the more potent proinflammatory effect of these products with the risk of increasing perifocal edema.
- Mistletoe therapy should not be used if intracranial pressure is elevated or increasing!
- If there is a risk of increased intracranial pressure, specifically in malignant brain tumors with centralized location, Helixor® A may only be used with adequate anti- edematous therapy and close clinical monitoring.
- A combination with Boswellia serrata, e.g. frankincense extract capsules 3x daily 1,200 mg (e.g. 4 capsules of 300 mg) p.o. to reduce brain edema and for additive tumor inhibition is highly recommended on the basis of existing experience and first study data (www.boswellia.org).
- The combination with Helleborus niger aquos. (Helixor)* D12 à D3 3x weekly 1 ampoule SC in daily rotation with Helixor® A has proven itself and is the standard therapy for brain tumors in Anthroposophic Medicine. Higher potencies are preferred if psychological symptoms dominate, lower potencies in case of pronounced brain edema. The latter also demonstrate a good effect on memory and concentration disorders following brain radiotherapy.

Brain Tumors and Brain Metastases (cont.)

BRAIN TUMORS AND BRAIN METASTASES

Selection of type: Helixor® A

Injections:

- 3x weekly (e.g. Monday, Wednesday, Friday) for relapse prevention following radical surgery as well as for inoperable, but slowly growing, histologically benign brain tumors.
- Daily for inoperable or palliative surgically treated malignomas of the CNS (exception: for combination with Helleborus niger every 2nd day, with daily rotation with Helleborus).
- Preferred upper arms and shoulder/neck region
- If the patient administers the injections him/herself: abdomen and upper thighs

TREATMENT SCHEDULE

Induction Therapy:

1x SE I ► 1x SE II ► 1x SE IV ► 1x SE IV + 1 amp. of 50 mg

i.e. One ampoule of 50 mg is drawn with each ampoule of the SE IV (resulting in: 70 mg, 70 mg, 80 mg, 80 mg, 100 mg, 100 mg, 100 mg).
During chemotherapy or radiotherapy, a slower dose increase with OP is recommended in place of SE (see page 41).

Maintenance Therapy:

- 100 mg / 150 mg / 200 mg at 3x weekly injection
- Or 100/100/150/150/200/200/200 mg at daily injection

Therapy Pauses:

- Progressive metastasizing tumors: no pause
- Following resection of metastases, with present absence of tumors: 1-2 weeks pause after 4 weeks of therapy
- For remission lasting over 3 months or growth stagnation: careful attempt with 1-2 weeks pause following every 4 weeks of therapy

If this treatment does not result in improvement within eight weeks, or if there are signs of tumor progression, we recommend trying a stepwise dose increase to a maximum of 400 mg daily, best also with rhythmic dosing.

Brain Tumors and Brain Metastases (cont.)

Injections:

- 100 mg / 150mg / 200 mg at 3x weekly injection
- Or 100 / 100 / 150 / 150 / 200 / 200 / 200 mg at daily injection

Therapy Pauses:

- Progressive metastasizing tumors: no pause
- Following resection of metastases, with present absence of tumors: 1-2 weeks pause after 4 weeks of therapy
- For remission lasting over 3 months or growth stagnation: careful attempt with 1-2 weeks pause following every 4 weeks of therapy

If this treatment does not result in improvement within eight weeks, or if there are signs of tumor progression, it's recommended to try a stepwise dose increase to a maximum of 400 mg daily, best also with rhythmic dosing.

Sarcomas

In general, the treatment principles described on page 39 for solid malignomas apply. From experience, sarcoma patients do not respond quite as well to mistletoe therapy as do carcinoma patients in terms of tumor-inhibiting effects. The lower the degree of malignancy and the older the patient, the better the response to mistletoe therapy appears to be. To increase the effectiveness of mistletoe therapy one can consider the additional subcutaneous injection of Helleborus niger aquos. (Helixor) D6 à D3 2 – 3x weekly 1 ampoule on the injection-free days of mistletoe therapy.

Selection of type: Helixor® P

Exception: Situations where Helixor® A is recommended as a matter of principle (see page 26)

Injections:

- 3x per week (e.g. Monday, Wednesday, Friday)
- Changeover to daily injection in case of rapid progression, lack of success of the 3x weekly injection or worsening of the state of health on injection-free days

Treatment Schedule:

Depending on UICC stage according to the treatment schedule for solid malignomas (see page 39).

In sarcomas one should note that the stage classification for bone and soft tissue sarcomas is mainly dictated by the degree of malignancy (G1 – 4), whereas the size and extent of the primary tumor (T1 – 4) plays a subordinate role. Not only distant metastases are classified as stage IV, but also lymph node metastases.

Malignant Systemic Diseases

In case of malignant systemic diseases (malignant lymphomas, plasmacytomas, leukemias, myeloproliferative and myelodysplastic syndrome), mistletoe therapy plays a less important role compared with carcinomas as far as the integrated oncological therapeutic concept is concerned. Nonetheless, good experiences have been made with the Helixor® coniferous mistletoe products (Helixor® A and Helixor® P) as adjuvant therapy in these diseases, for which the Helixor® products were originally developed specifically by the non-profit Association for Leukemia and Cancer Therapy.[16, 42, 43, 49, 51, 123, 124, 130, 160, 161, 165]

The benefit of adjuvant mistletoe therapy lies mainly in the improvement of quality of life. Experience has shown that fatigue, poor performance, night sweats and weight loss in particular, can be improved. The susceptibility to infections, which is very pronounced in these diseases, can often be reduced. The adverse reactions of chemotherapy and radiotherapy (especially bone marrow depression and immunosuppression) can also be reduced significantly in these diseases.

Nonetheless, numerous parties still caution against the use of mistletoe therapy in malignant systemic diseases, based on the assumption that mistletoe injections could lead to a stimulation of malignant degenerated immune cells. These cautions are based on an in vitro study as well as animal experiments with isolated mistletoe lectins, which could not be replicated either with mistletoe lectin or mistletoe extracts such as Helixor®.[9] Quite to the contrary, studies with Helixor® A, M and P on human lymphoma, myeloma and leukemia cell lines demonstrated distinct to significant inhibitory effects in vitro and also in animal models.[9, 33, 34, 52, 62, 64, 68, 118, 123, 124, 131]

Defined Precancerous Conditions

Diseases or changes in tissue which are statistically associated with an increased risk of degeneration are termed precancerous conditions. Some authors also refer to the carcinoma in situ as a precancerous condition although the current international use of language defines this as a preinvasive carcinoma (stage 0).

Helixor® therapy is justified when complete surgical resection is not possible or not required, or is expressly refused by the patient, and where regular monitoring is assured.

In case of a high risk of relapse, e.g. in ductal carcinoma in situ, relapse prevention following surgery is also advisable (see page 42).

Facultative Precancerous Conditions
Malignant degeneration occurs in less than 30 % of cases, and this usually after more than 5 years.

Obligate Precancerous Conditions
Transition to a malignant tumor occurs relatively often here (over 30 %) and also quickly (in less than 5 years).

Note: The difference between facultative and obligate precancerous conditions is partially blurred and differs depending on the literature. This differentiation is not made in the Anglo-Saxon literature. This does not play a crucial role for 4 with Helixor® as it only gives a statistical degeneration risk, which does not allow any conclusions with regard to specific individual cases.

Defined Precancerous Conditions (cont.)

Selection of type: see pages 23 and 77

Injections:

- 2 - 3x per week
- As close as possible to the precancerous site

TREATMENT SCHEDULE

Induction Therapy:

1x SE I ▶1x SE II ▶2 weeks pause

Maintenance Therapy:

1x SE II ▶1x SE II ▶2 weeks pause

Duration of Therapy: initially 6 months

Therapy Pauses: initially 6 months

If regular controls show an improvement in pathological findings, or at least unchanged findings, then the pauses should be extended gradually: initially to 4, then to 8 weeks.

As long as the precancerous condition persists, at least 4 SE should be administered as prophylactic cure per year (see page 31) – until completely subsided.

Pharmaceutical Principles

Development of the Helixor® Mistletoe Products

Approved according to AMG (German Medicines Act) – safe and effective

Manufacturing Process

Standardized process from the harvest to the ampoule

Development of the Helixor® Mistletoe Products

The white-berry mistletoe (Viscum album L.), a semi-parasite which grows on trees and bushes, has been known as a medicinal plant since antiquity. Among others, it was used to treat splenomegaly, epilepsy, arteriosclerosis, hypertension and rheumatic diseases. Its use in tumors was first described in 1917 by Dr. Rudolf Steiner. Anthroposophic Medicine, which he developed jointly with physician Dr. Ita Wegman, does not regard itself as an alternative to conventional scientific medicine, the principles of which are fully accepted, but as an opportunity for an insight-based as well as therapeutic extension.

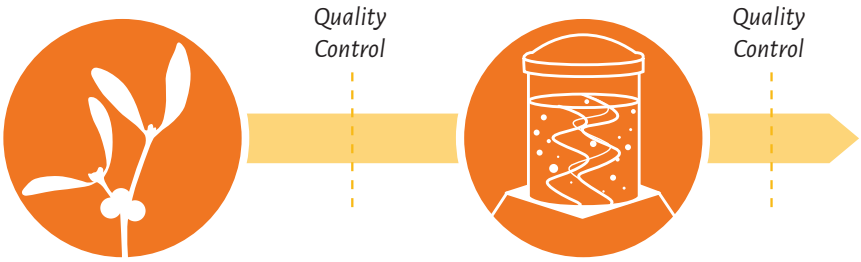
Helixor® mistletoe therapy is not an alternative to conventional therapies, but a salutogenetic therapeutic concept embedded within integrative oncology.

Helixor® mistletoe products were developed in the 1970s by the non-profit Association for Leukemia and Cancer Therapy in an attempt to improve the therapeutic success with Viscum album through a new manufacturing process. Since 1975, manufacturing and marketing are in the hands of Helixor Heilmittel GmbH. Since 1982, the Helixor® products have been approved in Germany in accordance with the Medicines Act. This was followed by approvals in numerous other countries.

Meanwhile, more than 250 publications have appeared on Helixor® – including 78 publications on 39 clinical studies, 32 PhD and diploma theses, and numerous papers on ingredients, mode of action and clinical experience (for selected literature see page 75).

The production building at the Fischermühle in Rosenfeld, Germany

Manufacturing Process of Helixor® Mistletoe Products

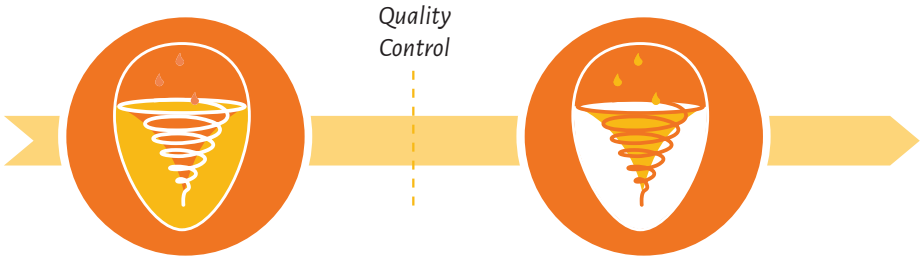


1. Harvest

The mistletoe is harvested from the trees four times a year, handpicked, ground, and stored in freezing temperatures.

2. Extraction

The mistletoe material - separated according to summer and winter harvests - is extracted.

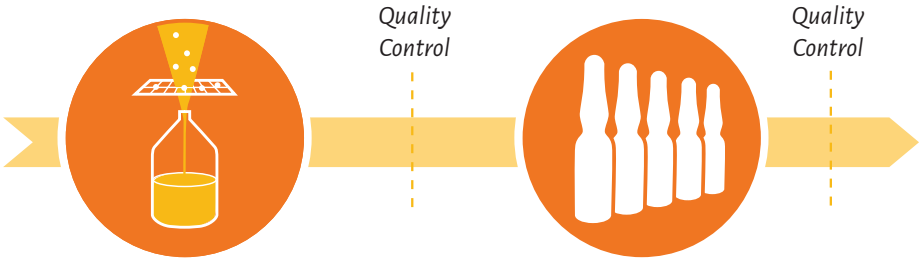


3. Mixing

The summer and winter extracts are combined to Helixor® 50 mg/ml in a special Helixor® mixing process.

4. Dilution

Further concentrations are produced by diluting Helixor® 50 mg/ml.

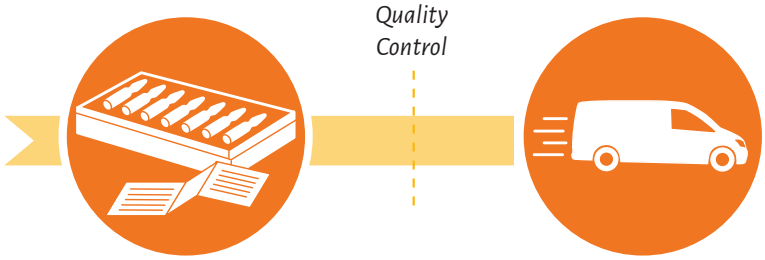


5. Sterile Filtration

For intermediate storage, the product is sterile filtered and filled into bottles in the cleanroom.

6. Ampoule Filling

Helixor® is filled with 1 ml or 2 ml ampoules in the cleanroom.



7. Packaging

The ampoules are packed country-specific for worldwide distribution.

8. Shipping

Dispatch of individual orders.

The entire manufacturing complies with the European Union GMP Guidelines and is accompanied by strict quality controls.

Manufacturing Process

For the manufacturing of our Helixor® medicinal products we process the mistletoes Viscum album ssp. album (deciduous tree mistletoe), Viscum album ssp. abietis (fir mistletoe) and Viscum album ssp. austriacum (pine mistletoe). Each type of mistletoe is harvested four times a year (winter, spring, summer, fall) to include the entire development cycle of the mistletoe through the year in the whole plant extract. The harvest areas are in remote locations far away from industrial and traffic emissions. The young parts of the plant are used, bearing berries or blossoms, depending on the time of year.

Aqueous extraction is carried out separately for the summer and winter harvests of each type of mistletoe. The fresh and finely ground plant is swirled rhythmically in hypotonic saline solution. This results in a 5 % extract which is preserved through sterile filtration. Sterile filtration enables gentle conservation without using heat or additives.

The summer and winter extracts are mixed at a ratio of 1 : 3 in a Helixor-specific swirling process to give a mixture of Helixor® 50 mg and isotonized by adding sodium chloride. This swirling process lent itself to the name Helixor® (composed of the Greek words helix = spiral and ixos = mistletoe).

Converted, Helixor® 50 mg contains the extract from 50 mg of fresh plant in 1 ml, which equates to a drug-extract ratio of 1 : 20. This Helixor® 50 mg is used for manufacturing the dilutions in a further process step – again by applying the swirling process – where it is diluted with the appropriate of distilled water and isotonized by adding NaCl. In the final manufacturing stage, the various concentrations are sterile filtered and filled into 1 ml or 2 ml (Helixor® 100 mg) ampoules.

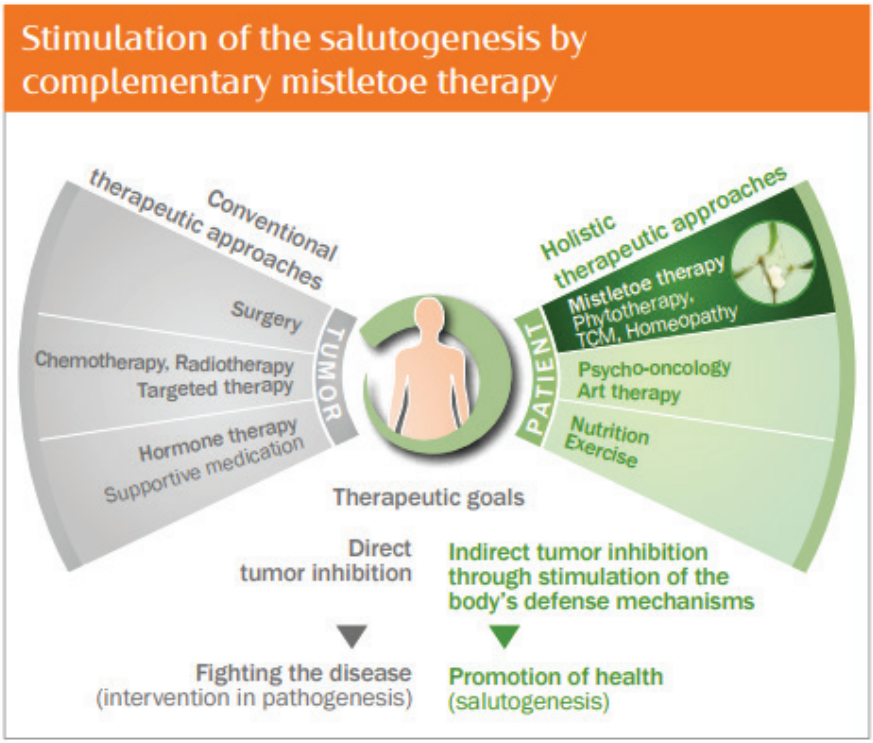
Concept of Integrative Oncology

Combination With Other Drugs and Types of Therapy

Other supportive therapeutic measures

Combination with Other Drugs and Types of Therapy

The effectiveness of mistletoe therapy with Helixor® can be increased significantly if it is embedded in an appropriate overall therapeutic concept. Considering the objective of creating a new balance between the human organism and the tumor, those methods should be selected from among the available conventional and biological therapeutic possibilities which are appropriate to the individual situation of the patient and where their modes of action complement each other in a useful manner.



Combination with Conventional Oncological Therapeutic Methods

Mistletoe therapy with Helixor® is not an alternative, but rather it complements standard oncological therapy. Whereas this is directed at the elimination or inhibition of the tumor cells, mistletoe therapy is intended to activate the body's own processes to limit tumor growth and normalize disturbed functions, thus supporting the body in its fight against cancer.

- **Surgery**, as an effective localized measure, is usefully complemented by systemicacting mistletoe therapy when given postoperatively, and ideally already preoperatively, as relapse prevention or adjuvant therapy (see page 43).

- In as far as **chemotherapy** is indicated, a combination with Helixor® also proves of use here, as Helixor® counteracts the immunosuppressive and myelodepressive effects of cytostatics and improves their subjective tolerability without negatively affecting their effectiveness. In fact, there are indications of synergistic effects.[19, 22] Here, Helixor® is given both during chemotherapy (including therapy pauses) as well as after completion of cytostatic treatment to stabilize the success of treatment and as relapse prevention. Helixor® A is preferred during chemotherapy due to its pronounced immunoprotective and DNA-stabilizing effects.

Combination with Conventional Oncological Therapeutic Methods (cont.)

- Helixor® A is also a useful complement when radiotherapy is required, as it can improve the tolerability and effectiveness of radiotherapy.[3, 70, 83]

- The combination with hormone therapy has proven itself in metastasizing breast, uterine or prostate cancer. Whereas chemotherapy considerably impairs the inflammatory and immunostimulating effect of mistletoe therapy, this is hardly the case in hormone therapy.

- Clinics and oncological practices with considerable expe- rience in mistletoe therapy often also combine this with targeted therapies, with no signs of interactions. With a view to the highly targeted pharmacological intervention of targeted therapies, no theoretical interactions with the known cytotoxic, immunomodulating and DNA-protective effects of Helixor® can be expected.

- For dose adjustment in chemotherapy and radiotherapy see page 34.

Combinations Not Recommended with Helixor®

All drugs which suppress the acute inflammatory reaction to Helixor® should be avoided if possible, in as far as there are alternatives. Specifically this relates to:

- **Antipyretics**: Fever should not be suppressed if possible as the body's defense mechanisms perform best at 39 – 40 °C (^= 102 – 104 °F). If the fever exceeds a tolerable level, the temperature should initially be lowered by applying conventional physical measures (e.g. leg compresses).

- **Antiphlogistics and antirheumatic agents** (steroidal or non-steroidal): Avoid their use if possible, with the exception of vital indications, for example, corticosteroids in brain edema or as part of chemotherapy protocols. As an alternative to corticosteroids one may consider Helleborus niger aquos. at low potency or frankincense extract (see page 54).

- **Peripherally acting analgesics** (e.g. acetylsalicylic acid): A trial with centrally acting analgesics (e.g. tilidine, tramadol) is advisable initially in tumor pains and as far as necessary. In many cases (e.g. spasmodic abdominal pain), spasmolytics or external administrations such as camomile abdominal compresses are useful. Experience has shown that the need for analgesics is reduced considerably through timely administration of mistletoe therapy.

- **Immunosuppressives**: Helixor® should not be combined with immunosuppressives which are, for example, necessary for the treatment of autoimmune diseases or following organ transplants, to avoid a theoretically possible weakening of the immunosuppressive effect. In combination with other immunomodulating substances (interferons, thymus preparations and others) an increase in both the desired and undesired effects is theoretically possible. The combination should therefore be avoided or careful dosing of Helixor® with meticulous therapy monitoring is recommended.

In **combination with other immunomodulating substances** (interferons, thymus preparations and others) an increase in both the desired and undesired effects is theoretically possible. The combination should therefore be avoided or careful dosing of Helixor® with meticulous therapy monitoring is recommended.

Supportive Therapeutic Measures

Of the many useful adjunctive measures available, only the most important ones can be mentioned briefly in this brochure. Many of these require consultations with physicians and the active cooperation of the patient.

- **Drug treatments**

- **Other winter bloomers to complement and support mistletoe therapy**: Dr. Rudolf Steiner pointed out that antitumor properties can also be expected of other winter bloomers such as Helleborus. This has proven to be the case in as far as specific apoptosis-induced effects have also been proven for Helleborus niger in lymphoma, leukemia, sarcoma and melanoma cell lines, and sound clinical evidence has meanwhile been reported.* Helleborus is worth considering alternating with mistletoe therapy, particularly in atypical tumors with fever, pronounced inflammatory symptoms and edemas, especially in highly advanced solid tumors with cachexia, but also in all malignant systemic diseases. With regard to the Helleborus species, Helleborus niger is advisable in particular for brain tumors and tumors of the urogenital system, but also in cases of pronounced psychological symptoms with anxiety, depression and impaired vigilance. Good experience has also been reported for Helleborus niger in lung cancer (also as inhalation therapy) and malignant systemic diseases, but here one should also consider Helleborus foetidus, which has a more potent cytotoxic effect on leukemic cells in vitro than Helleborus niger.*

- Evidence on antitumor effects for low Colchicum (autumn crocus) potencies is also available, and good experience has been gained specifically in childhood leukemias and malignant lymphomas, particularly in cervical lymph node swelling.

- The additional administration of Carduus marianus is recommended to **support liver function** – especially for tumors in the digestive tract, liver metastases or during and after chemotherapy.

- Horsetail, stinging nettle, yarrow and dandelion teas can be considered for **cleansing**, **detoxification** and general **metabolic activation**.

- To **improve lack of appetite**, **nausea**, **fullness**, Amara drops 3x daily 15 – 20 drops.

- For **nausea and vomiting** Nux vomica D4 4x daily to every half hour 7 – 12 drops in water.

- For the **localized therapy of mucositis** Ratanhia comp. solution or Propolis tincture 3x daily 15 drops in water for oral rinsing, then apply undiluted to aphthae with a cotton swab.

- For **menopausal complaints** Cimicifuga racemosa both in breast cancer and prostate cancer patients.

- Other medications proven in the biological treatment of cancers, in as far as indicated, such as **enzymes**, **organ preparations**, **minerals**, **(e.g. selenium) and vitamins.**

Thymus preparations and other immunostimulating medicines (e.g. interferon) should, as a rule, not be given in parallel with mistletoe therapy, but alternating, to avoid exhaustion or overburdening of the immune system. More in this case does not necessarily mean more efficacy!

Supportive Therapeutic Measures (cont.)

- **Hyperthermia**: Both locoregional depth hyperthermia for inoperable tumors or metastases, as well as whole body hyperthermia for metastasizing tumors, are ideal complements to mistletoe therapy in the sense of increasing the effectiveness of fever-like immunological effects, while at the same time providing improved circulation and increased vulnerability of the tumor cells. Passive hyperthermia can be employed when active hyperthermia (fever therapy) with mistletoe products no longer induces a fever reaction after several administrations. The reverse is also true, as there is evidence that patients with an inadequate rise in temperature under hyperthermia achieve better results with simultaneous mistletoe therapy. Here it has proven useful to administer the so-far maximum dose of Helixor® subcutaneously on the evening prior to hyperthermia (e.g. 100 – 200 mg Helixor® M) and to administer a Helixor® infusion prior to or during the warming up and maintaining of temperature.

- **Stimulation of the thermoregulation**
  - Avoid heat loss through adequate clothing
  - Dosed physical activity (30 min. daily or 1 hour every 2nd day; avoid fatigue)
  - Physiotherapy (e.g. alternating foot bath or shower)
  - Fever therapy

- **Modifying diet and lifestyle**
  - Change to as wholesome, varied and lacto-vegetable as possible diet rich in vegetables, fruit and whole grain (organic products preferred). If this is not possible for reasons of illness, then substitution of important vitamins and trace elements should be considered.
  - Avoid nicotine and alcohol
  - Stool regulation via natural means (if required)
  - Ample outdoor exercise
  - Rhythmic lifestyle with regular meals, approximately 7 hours of sleep and a short rest at midday
  - Avoid overexertion and air travel (this applies particularly to patients with advanced disease)

- **Develop new fields of interest and points of view**
  - Art therapy (e.g. painting, music) as a form of "conversation-free psychotherapy" and to awaken creative initiatives. There is considerable experience in Anthroposophic Medicine leading to an individual indication of suitable artistic therapeutic methods, often leading to amazing therapeutic results.
  - Stimulation to conscious experience of nature and art

- **Psycho-oncology**
  - Stimulation towards spiritual disease management and occupying oneself with the question as to the individual purpose of life

Appendix

Directory of Keywords

Selected Literature on Helixor®

Recommendation for Type Selection

For the most frequent types of tumors

Directory of Keywords

Directory of Keywords (cont.)

Directory of Keywords (cont.)

Directory of Keywords (cont.)

Directory of Keywords (cont.)

Selected Literature on Helixor®

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Selected Literature on Helixor® (cont.)

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Helixor® Type Recommendation

for the most common types of tumors

Please make sure to observe in which cases Helixor® A should preferably be used, regardless of the type of tumor (*see page 32*).

Head/Neck Region	Type
Astrocytoma	**Abietis**
Brain Tumors	**Abietis**
Eye Cancer	**Abietis**
Glioblastoma	**Abietis**
Laryngeal Cancer	**Abietis**
Lip Cancer	**Abietis**
Meningioma	**Abietis**
Oral Cancer	**Abietis**
Pharyngeal Cancer (oropharynx and hypopharynx)	**Abietis**
Salivary Gland Cancer	**Abietis**

Respiratory Tract	Type
Lung Cancer	**Abietis**
Pleural Mesothelioma	**Abietis**
Tracheal Carcinoma	**Abietis**

Mammary	Type
Breast Cancer Slim/Premenopausal	**Pini**
Breast Cancer Obese/Postmenopausal	**Mali**

Digestive Tract	Type
Ampulla of Vater Cancer	**Mali**
Anal Cancer	**Mali**
Appendix Cancer	**Mali**
Cholangiocarcinoma	**Mali**
Colon Cancer	**Mali**
Esophageal Cancer	**Abietis**
Gallbladder Cancer	**Mali**
Hepatocellular Carcinoma	**Mali**
Liver Cancer	**Mali**
Pancreatic Cancer	**Mali**

Helixor® Type Recommendation

for the most common types of tumors (cont.)

Please make sure to observe in which cases Helixor® A should preferably be used, regardless of the type of tumor.

Digestive Tract (cont.)	Type
Small Intestine Cancer	**Mali**
Stomach Cancer	**Mali**

Digestive Tract (cont.)	Type
Bladder Cancer	**Mali**
Cervical Cancer	**Mali**
Chorionic Carcinoma	**Mali**
Endometrial Cancer	**Mali**
Ovarian Cancer	**Mali**
Penile Cancer	**Pini**
Prostate Cancer	**Abietis**
Rectal Cancer	**Mali**
Renal Cell Carcinoma	**Pini**
Testicular Cancer	**Pini**
Transitional Cell Cancer of the Renal Pelvis and Ureter	**Mali**
Uterine Cancer	**Mali**
Vaginal Cancer	**Mali**
Vulvar Cancer	**Mali**

Endocrine System	Type
Adrenal Cancer	**Pini**
Thyroid Cancer	**Abietis**

Skin	Type
Malignant Melanoma	**Pini**
Skin Cancer	**Pini**

Sarcoma	Type
Osteosarcoma	**Pini**
Soft Tissue Sarcoma	**Pini**

Additional Resources

https://medsektion-goetheanum.org/forschung/investigating-clinical-fields/cancer-disease-mistletoe-treatment/

https://paam.wildapricot.org/resources/Pictures/Kienle_MistletoeSummary2014_vmo-1.pdf

https://paam.wildapricot.org/Mistletoe

https://www.cancer.gov/about-cancer/treatment/cam/patient/mistletoe-pdq