1. Name of the medicinal product

Helixor® A 0.01 mg
Helixor® A 0.1 mg
Helixor® A 1 mg
Helixor® A 5 mg
Helixor® A 10 mg
Helixor® A 20 mg
Helixor® A 30 mg
Helixor® A 50 mg
Helixor® A 100 mg

Active substance: extract of fir mistletoe
Solution for injection

Helixor® M 0.01 mg
Helixor® M 0.1 mg
Helixor® M 1 mg
Helixor® M 5 mg
Helixor® M 10 mg
Helixor® M 20 mg
Helixor® M 30 mg
Helixor® M 50 mg
Helixor® M 100 mg

Active substance: extract of apple tree mistletoe
Solution for injection

Helixor® P 0.01 mg
Helixor® P 0.1 mg
Helixor® P 1 mg
Helixor® P 5 mg
Helixor® P 10 mg
Helixor® P 20 mg
Helixor® P 30 mg
Helixor® P 50 mg
Helixor® P 100 mg

Active substance: extract of pine mistletoe
Solution for injection

2. Qualitative and quantitative composition by active substances

1 ampoule of 1 ml contains:

Active substance: extract of fresh fir mistletoe/apple tree mistletoe/pine mistletoe
(ratio of plant to extract = 1 : 20) x mg

Extraction agent: water for injection, sodium chloride (99.91 : 0.09)

Name of the medicinal product and strength
Helixor® A/M/P 0.01 mg
Helixor® A/M/P 0.1 mg
Helixor® A/M/P 1 mg
Helixor® A/M/P 5 mg
Helixor® A/M/P 10 mg
Helixor® A/M/P 20 mg
Helixor® A/M/P 30 mg
Helixor® A/M/P 50 mg

The strength stated in mg indicates the amount of fresh plant material which was used to manufacture 1 ampoule of Helixor® A/M/P. For example: One ampoule “Helixor® 1 mg” contains the extract of 1 mg of fresh mistletoe.

For the complete list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

4. Clinical particulars

4.1 Therapeutic indications

According to the anthroposophic knowledge of man and nature.

Including:
In adults: the stimulation of forming and integrating forces for the dissolution and reintegration of autonomous growth processes, e.g.:
- Malignant tumor diseases, also with concomitant disorders of the hematopoetic system
- Benign tumor diseases
- Defined precancerous conditions
- Prevention of recurrence following tumor surgery

4.2 Dosage, method and duration of administration

Induction phase
Unless prescribed otherwise, treatment begins with one ampoule of 1 mg Helixor® A, M or P. If, in rare cases, excessive local reactions or fever occur after administering 1 mg Helixor®, the dose is temporarily reduced to 0.1 mg or 0.01 mg Helixor®. If tolerability is good, the dose is gradually increased until the optimum dose is achieved. The dose can be gradually increased by means of series packs (SE I, followed as needed by SE II and SE IV) or original packs of 1, 5, 10, 20, 30, 50 and 100 mg Helixor®

Maximum daily dose: 400 mg Helixor® SC

Please see also the recommended treatment schedules on the last page of this summary; they are compiled from many years of clinical experience.

The optimum dose must be determined on an individual basis. According to current knowledge, the following reactions may occur, either individually or in combination.

a) Changes in subjective well-being
If side effects such as fatigue, chills, a general feeling of malaise, headache, and brief spells of dizziness occur on the day of the injection, this is not a sign of poor tolerability. Instead, it indicates that the dose is effective and perhaps even too high. If these symptoms have not resolved by the next day, or if they exceed tolerable limits, the concentration (dose) should be reduced.

Signs that the optimum dose has been achieved include an improvement in general well-being (increase in appetite and weight, normalization of sleep rhythm, feeling of warmth and ability to perform) and in emotional states (better mood, increase in the will to live, a sense of drive) as well as pain relief.

b) Temperature reactions
An above-average increase in body temperature a few hours after the injection, restoration of the physiological difference of at least 0.5 °C/0.9 °F between morning and evening body temperature, or an increase in average body temperature during treatment.

By contrast, if a tumor-related fever is present, low doses are used to normalize body temperature and restore its natural rhythm.

c) Immunological reactions
These include an increase in leukocytes (primarily the absolute lymphocyte and eosinophil count), and an improvement in cellular immune status in the recall antigen assay or in lymphocyte subpopulations.

d) Local inflammatory reactions
Local inflammatory reactions of up to 5 cm diameter at the injection site.

Maintenance phase
Unless prescribed otherwise: Continue treatment with the optimum dose that was individually determined. To prevent habituation a rhythmic administration is recommended:
- Alternating with lower doses, via increasing and possibly also decreasing dosage series
- Administering the injections in consistent patterns, such as on days 1, 2 and 5 of each week
- Introducing pauses, e.g. a pause of 1 – 2 weeks after 4 weeks of treatment

After longer pauses in treatment (four weeks or more), the dose should initially be reduced by half, as a precaution.

The dosage should be verified at intervals of 3 – 6 months, taking into account the patient’s reaction as well as the tumor status.

Frequency of administration
Unless prescribed otherwise: one subcaneous injection 1 – 3 times a week, and in special cases daily injections (see treatment schedules, last page).

Information on dosage
In cases of pronounced allergic diathesis, a lower initial dose (0.01 mg) is indicated, as is a delayed dose increase, e.g. by using original packs.

During radio- or chemotherapy, a dose reduction may be necessary, due to changes in the patient’s reactions.

Dosage for patients with impaired kidney function
There is not enough data available to provide specific dosage recommendations for patients with impaired kidney function. To date, general experience has not indicated that dosage needs to be adjusted.

Method of administration
Subcutaneous injection, if possible near the tumor or metastasis. If this is not possible, select varying sites (such as the abdomen, upper arm, upper thigh). Do not inject in inflamed sites or radiation fields. Injections must be strictly subcutaneous.

September 2018
Helixor® A/-M/-P

Summary of Product Characteristics

As a precaution, Helixor® is not to be combined with other drugs in the same syringe (see also section 6.2).

Do not store opened ampoules for later use.

Duration of administration
The attending physician decides the duration of administration.

There is no general limit on the duration of administration. It is determined by the physician and is based on each patient’s individual risk of recurrence, well-being, and findings. Treatment should last several years. As a rule, pauses of increasing length are introduced.

4.3 Contraindications
- Known allergies to mistletoe preparations
- Acute inflammatory or highly febrile diseases: treatment is to be interrupted until the inflammatory symptoms resolve
- Chronic granulomatous diseases, and florid autoimmune diseases or those under immunosuppressive therapy
- Hyperthyroidism with tachycardia

4.4 Special warnings and precautions for use
In patients with allergies, dosage must be selected with particular caution, and close monitoring is indicated (see also “Information on dosage”).

Primary brain and spinal cord tumors, or brain metastases with the risk of increased intracranial pressure: In these cases, the products should only be administered with clinical monitoring.

The ampoule should be briefly warmed in the hand, since there have been reports of cold agglutinins forming after IV administration of mistletoe injection solutions below body temperature.

Helixor® contains less than 1 mmol sodium per dose, i.e. it is practically sodium-free.

4.5 Interaction with other medicinal products
No studies have been done on interactions with other immunomodulating substances (such as thymus extracts). If these products were used in the recent past, careful dosage and monitoring of suitable immune parameters is recommended.

4.6 Administration during pregnancy and lactation
No adequate animal studies are available on the effects on pregnancy, embryonic/fetal development, birth and postnatal development, particularly hematopoiesis and the immune system of the fetus/infant (see section 5.3). The potential risk to human life is unknown. Caution is advised in administering Helixor® during pregnancy or lactation.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Adverse reactions
A slight increase in body temperature and local inflammatory reactions at the subcutaneous injection site occur almost regularly at the beginning of treatment and are evidence of the patient’s therapeutic response. Temporary minor swelling of regional lymph nodes is also harmless.

In case of fever over 38 °C/100.4 °F develops (possibility with fatigue, chills, general malaise, headache, and brief spells of dizziness) or larger local reactions of over 5 cm diameter, the next injection should not be given until after these symptoms resolve, and it should be given at a lower strength or dose.

The fever caused by a Helixor® injection should not be treated with an antipyretic. If the fever lasts longer than three days, an infectious process or tumor fever should be considered.

Excessive local reactions can be prevented by using a lower strength or a smaller quantity of Helixor®. In such cases, administration of 0.1 – 0.5 ml Helixor® is recommended, using a calibrated 1 ml syringe.

Localized or systemic allergic or allergic reactions can occur (usually as generalized pruritus, urticaria or exanthema, which may include Quincke’s edema, chills, shortness of breath, and bronchospasm; individual cases include shock or erythema multiforme). In such cases, treatment must be discontinued and medical treatment is necessary.

Previously existing inflammations may be activated, and superficial phlebitis near the injection site may occur. If so, treatment must be temporarily interrupted until the symptoms resolve.

Chronic granulomatous inflammations (sarcoidosis, erythema nodosum) and autoimmune diseases (dermatomyositis) have been reported during mistletoe therapy. Reported symptoms have also included increased intracranial pressure among patients with brain tumors or brain metastases during mistletoe therapy.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after marketing authorization is of great importance. This enables the benefit/risk balance of the medicinal product to be monitored continuously. Medical professionals are asked to report any suspected case of adverse reactions to the following authority:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn, Germany
www.bfarm.de

4.9 Overdose/excessive reaction: symptoms, emergency measures, antidotes

In case of local inflammatory reactions of over 5 cm diameter, fever, or flu-like symptoms, the next injection should not be given until after these symptoms resolve, and it should be given at a significantly lower dose.

Occurrence of anaphylactic reactions
Signs of a beginning or advanced anaphylactic reaction include itching or burning on the palms or soles of the feet, tongue and palate, itching, erythema and urticaria on the skin and mucous membranes. In the course of time, nausea, cramps, vomiting, rhinorrhea, hoarseness, dyspnea, tachycardia and a drop in blood pressure may occur, as well as shock and circulatory arrest.

Emergency treatment of the anaphylactic reaction is carried out according to the current guidelines. Adequate emergency equipment must be available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

High in vitro doses of Helixor® have been shown to have mild to moderate cytotoxic effects: they are the strongest in Helixor® P, the weakest in Helixor® M. Helixor® A has immunomodulating and DNA-stabilizing properties.

In animal studies, moderate to high doses of Helixor® have demonstrated antitumor, metastasis-suppressing and immunomodulating effects when administered intratumorally, peritumorally or intraperitoneally.

Immunomodulating properties (predominantly an increase of NK cells at low to moderate doses) have also been described in humans. Evidence of improvement in quality of life was found in a study with Helixor® A conducted in patients in China. An internationally recognized quality of life questionnaire (Functional Living Index - Cancer (FLIC)) which was validated for the Chinese language was used, as was the internationally used and validated Karnofsky Performance Index. The study was reviewed by the Institute of Medical Biometry and Informatics at the University of Heidelberg, Germany.

Pharmacotherapeutic group:
Other homeopathic and anthroposophic medicines, mistletoe
ATC code: L01CH01

5.2 Pharmacokinetic properties

Studies on pharmacokinetics and bioavailability were not conducted, for methodological reasons.

5.3 Preclinical safety data

Animal studies on acute (Helixor® A, M, P), subacute (Helixor® M) and subchronic toxicity (Helixor® A) yielded no toxic effects even at the maximum applicable dosage (500 mg/kg - acute; 450 mg/kg - subacute; 100 mg/kg - subchronic). Tests on bacterial strains (Amsalmonella/ microsome plate incorporation assay) showed no evidence of mutagenicity (Helixor® A, M and P).

In vitro experiments on mammal cells determined an increased incidence of chromosomal breakage at high concentrations of Helixor® M and P, but not Helixor® A.

MITT cytotoxicity assays of human liver cells showed cytotoxic effects at concentrations of 0.05 – 5 mg Helixor® A, M and P/ml solvent.

Tests on interactions with cytchrome P450 isoenzymes determined that Helixor® A, M and P had a moderate or minor non-dose-dependent inhibiting effect in individual cases (HA: CYP2A6, CYP2C9; HM: CYP1A1/2, CYP2A6, CYP2B6; CYP2C8, CYP2C9; HP: CYP1A1/2, CYP2C8, CYP2C9, CYP3A4).

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Animal studies on immunotoxicity in the murine model, which were conducted with Helixor® P 50 mg, the Helixor® product with the highest lectin level, showed no immunotoxically relevant influence on general and specific immunoparame-

eters, nor on the humoral and cellular immune response, for administered doses of up to the triple amount of the daily therapeutic maximum. In further animal studies, the triple amount of the daily therapeutic maximum of Helixor® P 50 mg suggested a reduced capability of resistance against murine melanoma cells.

No data is available on chronic toxicity, reproductive toxicity or carcinogenicity.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride, sodium hydroxide.

Additional water for injection in Helixor® 0.01 mg to 30 mg.

6.2 Incompatibilities

Unknown. As a precaution, Helixor® A, M and P are not to be combined with other drugs in the same syringe.

6.3 Shelf life

Helixor® 0.01 mg – 100 mg: 3 years

6.4 Special precautions for storage

Store the ampoules in the original packaging to protect the contents from light.

Helixor® 0.01 mg – 0.1 mg: Store in the refrigerator.

Helixor® 1 mg – 100 mg: Do not store at temperatures above 30 °C/86 °F.

6.5 Nature and contents of container

Helixor® is available in the following packs:

Original packs (OP) with 8 ampoules of the same concentration (0.01 – 100 mg)

Great packs (GP) with 50 ampoules of the same concentration (1 – 100 mg)

The following series packs (SE), each of 7 ampoules of increasing doses, are available for increasing the dose in induction therapy, as well as for maintenance therapy.

SE III is used instead of SE I and SE II if a more rapid dose increase is needed, especially in a hospital setting.

Series I Ampoules
Helixor® A/M/P 1 mg 3
Helixor® A/M/P 5 mg 3
Helixor® A/M/P 10 mg 1

Series II Ampoules
Helixor® A/M/P 10 mg 2
Helixor® A/M/P 20 mg 2
Helixor® A/M/P 30 mg 3

Series III Ampoules
Helixor® A/M/P 1 mg 1
Helixor® A/M/P 5 mg 2
Helixor® A/M/P 10 mg 3
Helixor® A/M/P 20 mg 1

Bundle packs (BP) of 28 (4 x 7) ampoules are also available for series II and IV.

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorization holder

Helixor Heilmittel GmbH
Fischermühle 1
72348 Rosenfeld
Germany

Tel.: +49 7428 935-0
Fax: +49 7428 935-102
E-mail: mail@helixor.com
www.helixor.com

Medical Advisory Service:
Tel.: +49 7428 935-344
Fax: +49 7428 935-709
E-mail: advice@helixor.com

8. Marketing authorization numbers

Helixor® A 0.01 – 0.1 mg: 1008.07.00 – 1008.08.00

Helixor® A 1 – 100 mg: 1008.00.00 – 1008.06.00

Helixor® M 0.01 – 0.1 mg: 27360.00.00 – 27360.01.00

Helixor® M 1 – 100 mg: 1015.00.00 – 1015.06.00

Helixor® P 0.01 – 0.1 mg: 1001.07.00 – 1001.08.00

Helixor® P 1 – 100 mg: 1001.00.00 – 1001.06.00

9. Date of renewal of the authorization

December 11, 2013

10. Date of revision of the text

September 15, 2018

11. Prescription status

Pharmacy-only
## TREATMENT SCHEDULES AS AN ORIENTATION GUIDELINE

The aspects of individual dosage must be taken into account (see section 4.2).

### Treatment schedule for malignant tumors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Induction Therapy</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – I*</td>
<td>SE I → SE II → 2 weeks pause</td>
<td>SE II twice in a row → 2 weeks pause Repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose increase from 1 to 30 mg/ three injections a week</td>
</tr>
<tr>
<td>II**</td>
<td>SE I → SE II → SE IV → 2 weeks pause</td>
<td>SE IV twice in a row → 2 weeks pause Repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose increase from 1 to 50 mg/ three injections a week</td>
</tr>
<tr>
<td>III***</td>
<td>SE I → SE II → SE IV → SE IV + OP 50 mg** → 2 weeks pause</td>
<td>SE IV + OP 50 mg** twice in a row → 2 weeks pause Repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose increase from 1 to 100 mg/ three injections a week</td>
</tr>
<tr>
<td>IV***</td>
<td>SE I → SE II → SE IV → SE IV + OP 50 mg** → (no breaks)</td>
<td>1st + 2nd inj.: 100 mg 3rd + 4th inj.: 150 mg 5th – 7th inj.: 200 mg*** Repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose increase from 1 to 200 mg***/ injections between three times a week and daily</td>
</tr>
</tbody>
</table>

### Treating defined precancerous conditions

To prevent recurrence postoperatively: see schedule above, stage 0 – I.
To treat inoperable precancerous conditions: see schedule above, stage III.

- SE = series pack
- OP = original pack
(For pack content, see section 6.5)

* UICC or FIGO stage; please see the TNM classification of malignant tumors.
** i.e., every ampoule of series pack IV is combined with one additional ampoule of 50 mg (for a total of 70/70/80/80/100/100/100 mg).
*** If another dose increase is necessary, it is carried out every two weeks in intervals of 50 mg, up to a maximum individual dose of 400 mg.