Summary of Product Characteristics

Helixor
Bringing life to life.

Helixor™ A / M

1. Name of the medicinal products

Helixor® A	1 mg	*not yet assigned*	Helixor® M	1 mg	*not yet assigned*
Helixor® A	5 mg	*not yet assigned*	Helixor® M	5 mg	*not yet assigned*
Helixor® A	20 mg	*not yet assigned*	Helixor® M	20 mg	*not yet assigned*
Helixor® A	50 mg	A7-2277L	Helixor® M	50 mg	AL-2279L
Helixor® A	100 mg	A7-2278L	Helixor® M	100 mg	AL-2280L

Active substance:
Aqueous extract of Viscum album Subspecies abietis ex herba recente, fir mistletoe

Active substance:
Aqueous extract of Viscum album subspecies album ex herba recente, apple tree mistletoe

2. Qualitative and quantitative Composition of the medicinal product

1 ampoule at 1 ml contains:

Active substance: Aqueous extract of *Viscum album*, drug to extract ratio (DER) = 1:20 x mg*
Excipients: Water for injection, sodium chloride (99,91 : 0,09)

Name and strength of the medical products		***x mg extract**
Helixor® A/M	1 mg	20 mg
Helixor® A/M	5 mg	101 mg
Helixor® A/M	20 mg	402 mg
Helixor® A/M	50 mg	1,006 mg

1 ampoule Helixor® A/M 100 mg at 2 ml contains:
Active substance: Aqueous extract of Viscum album, drug to extract ratio (DER) = 2.012 mg
Excipients: Water for injection, sodium chloride (99,91 : 0,09)

The strengths in mg refers to the amount of fresh mistletoe herbal substance employed for the production of 1 ampoule of Helixor® A/M; *e.g.* „Helixor® 1 mg“ contains in 1 ampoule the extract of 1 mg fresh mistletoe herbal substance.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solution for injection.
Ampoules with clear, colorless to yellow-brownish (acc. to strength) aqueous liquid.

4. Clinical Particulars

4.1 Therapeutic indications

Herbal medicinal product to be used in integrative oncology:
- Malignant tumors, also accompanied by disorders of the hematopoietic organs
- Prophylaxis of recurrence after tumor surgery
- Defined precancerous conditions
- Benign tumors

4.2 Posology and method of administration

Induction therapy

In adults: Unless otherwise prescribed, therapy starts with an ampoule of 1 mg. If well tolerated, the dose is increased stepwise up to the optimum dosage. For that purpose, packages with 6 ampoules each at 1, 5, 20, 50 und 100 mg can be used.

Maximum daily dose: 400 mg s.c.

Dose modification acc. to the patient's reaction

The optimum does has to be determined individually. For that purpose, according to the state of knowledge, the following reactions, emerging either individually or in combination, are to be considered.

a) Change in subjective well-being:
Symptoms, e.g. fatigue, chills, influenza-like symptoms, headache and transient attacks of dizziness that may occur on the day of injection are not signs of intolerance, but point to an effective dose, which may perhaps already be too high. If these symptoms have not resolved the following day or have become intolerable, the dose should be reduced.
An improvement in general well-being (increase in appetite and weight, normalization of sleep, feeling of warmth and functional capacity) and psychological well-being (brightening of mood, more initiative and courage to go on living) as well as a relief of pain are signs that the optimum dosage range is being used.

b) Temperature response:
A temperature response such as an above-average increase in body temperature some hours after injection, restoration of the physiological morning/evening difference of at least 0.5°C or an increase in the mean temperature level during treatment.
In case of tumor fever, the aim is to normalize body temperature and restore its normal rhythm by using low doses.

c) Immunological response:
For example increase in the leukocyte count (especially the absolute eosinophil and lymphocyte counts), improvement in the cellular immune status as revealed by Recall-Antigen-Test or by changes in the lymphocyte subpopulations.

d) Local inflammatory response:
Local inflammatory response up to max. 5 cm in diameter at the injection site.

Maintenance therapy

Unless otherwise prescribed: Treatment is continued with the individually established optimum dose.

Common maintenance doses:
- For palliative therapy in case inoperable or metastasizing tumors: 100-200 mg.
- For prophylaxis of recurrence, precancerous conditions and benign tumors: 20-50 mg.

In order to prevent the development of tolerance, rhythmic administration is recommended:
- Alternating the optimum dose with lower doses in the form of dosage series of increasing and possibly decreasing doses
- Rhythmical injection intervals, e.g. injection on the first, second and fifth days of a week.
- Inserting treatment-free pauses, e.g. 1-2 weeks pause after 4 weeks of therapy.

After treatment pauses of more than 4 weeks therapy should be resumed at half the normal dose as a precaution.

Dosage should be reviewed every 3-6 months on the basis of the response of the patient and of the tumor.

Frequency of administration

Unless otherwise prescribed, 2-3 x weekly; in special cases, daily.

Additional dosage instructions

In case of pronounced allergic diathesis, additional hyperthyreosis or autoimmune disease, Helixor A instead of Helixor M and a slow dose increase is indicated via subsequent administration of 2 packages of one strength, before the next strength is used.

Also during chemo- or radiation-therapy, a prolonged administration of one strength or a dose reduction can be indicated due to an altered responsiveness of the patient.

Dosage in case of impaired renal function: No sufficient data are available for a concrete dosage recommendation. To date, acc. to general experiences, dosage adaptation do not seem necessary.

Method of administration

Subcutaneous injection, if possible near to the tumor or metastasis, otherwise at constantly alternating sites (e.g. abdominal skin, upper arm or thigh). Do not inject into areas where the skin is inflamed or into radiation fields. Ensure the injection is strictly subcutaneous.

Do not mix Helixor® with other medicinal products in one syringe (see also 6.2 Incompatibilities).

Duration of administration

Duration of the treatment is, in principle, unlimited. It is determined by the physician and depends on the respective risk of recurrence and the individual condition or clinical course of the patient. It should last several years, generally with increasingly longer pauses.

4.3 Contraindications

- Known allergy to mistletoe preparations
- Acute inflammatory and highly febrile diseases: treatment should be interrupted until the signs of inflammation have subsided
- Florid autoimmune diseases and chronic-granulomatous diseases as well as such under immuno-suppressive therapy
- Hyperthyreosis with tachycardia

4.4 Special warnings and precautions for use

In allergic patients, take care of cautious dosage under particularly careful control (see: Additional dosage instructions).

Primary brain and spinal cord tumors or intracranial metastasis with the risk of increased intracranial pressure: In this cases, Helixor® should only be administered under sufficient anti-edematous therapy and tight clinical control.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, *i.e*. essentially "sodium-free".

4.5 Interactions with other medicinal products and other forms of interaction

For interactions with other immunomodulating substances (*e.g.* interferons, interleukins), no studies are available. In case of contemporary administration of respective products, a cautious dosage and control of immune parameters are advisable.

4.6 Fertility, pregnancy and lactation

There are no adequate animal studies with respect to effects on pregnancy, embryonal/fetal development, parturition and postnatal development, especially on hematopoiesis and the immune system in the fetus/infant (see section 5.3). The potential risk for humans is not known.

Usage during pregnancy and lactation with caution.

4.7 Effects on ability to drive and use machines

Helixor has no influence on the ability to drive or use machines.

4.8 Undesirable effects

A slight increase in body temperature and local inflammatory reaction at the subcutaneous injection site occur almost always at the beginning of therapy and are signs of the responsiveness of the patient. Equally harmless are slight transient swellings of the regional lymph nodes.

In case of fever above 38 °C (possibly with fatigue, chills, general malaise, headache and short dizziness) or larger local reactions of more than 5 cm in diameter, the next injection should not be administered before these symptoms have subsided, and a reduced strength should be given.

Fever induced by Helixor® injection should not be suppressed by antipyretic drugs. With persistent fever for more than 3 days, an infectious process or tumor fever should be considered.

Excessive local reactions can be avoided by using a lower strength or even a smaller amount of Helixor®. In this case, administration of 0.1-0.5 ml Helixor® is recommended using a graduated 1 ml syringe.

Localized or systemic allergic or allergoid reactions can occur (usually in the form of generalized pruritus, urticaria or rash, sometimes with Quincke's edema, chills, dyspnea and bronchospasm, in single cases with shock (1 case with simultaneous injection of a local anesthetic) or erythema multiforme), which require discontinuation of Helixor® and initiation of medical therapy.

Activation of preexisting inflammation and inflammatory irritation of superficial veins at the injection site are possible. Again, a temporary interruption of treatment until resolution of the inflammatory response is required.

There have been reports on chronic granulomatous inflammation (sarcoidosis, 3 cases; one of them with erythema nodosum, 1 case) and autoimmune diseases (dermatomyositis, 1 case) during mistletoe therapy.

Also symptoms of increased intracranial pressure in brain tumors/brain metastases during mistletoe therapy have been reported.

4.9 Overdose

In case of local inflammatory reaction over 5 cm in diameter, fever or flu-like symptoms, the next injection should be given only after resolution of these symptoms and at a significantly reduced dose.

For emergency treatment of anaphylaxis, the current guidelines have to be followed.

5. Pharmacologic Properties

5.1 Pharmacodynamic properties

For high doses of Helixor®, cytotoxic effects in vitro, immunomodulatory and DNA stabilizing properties could be shown.

In animal experiments, anti-tumoral, anti-metastatic and immunomodulating effects were confirmed under intra-and peritumoral as well as intraperitoneal administration of moderate to high doses of Helixor®.

In humans, there are also immunomodulating properties (mainly increase of NK cells under low to moderate dosage) described. Clinical studies show an improvement of the quality of life.

5.2 Pharmacokinetic properties

Studies on the pharmacokinetics and bioavailability of Helixor® were not performed due to methodological reasons.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity.

Animal experiments for acute, subacute and chronic toxicity, even at the maximal administrable dose of Helixor® (500 mg/kg-acute; 450 mg/kg-subacute, 100 mg/kg-subchronic) showed no toxic effects. Examination of bacterial strains via Ames-test showed no evidence of mutagenicity.

In vitro experiments in mammalian cells resulted in increased frequency of chromosome breakage at high concentrations of Helixor® M, but not Helixor® A, which can be explained by apoptosis induction.

In the MTT cytotoxicity assay using human liver cells, cytotoxic effects at concentrations of 0.05-5 mg Helixor®/ml were detected.

In studies of interactions with Helixor® and cytochrome P450 isoenzymes, in individual cases (HA: CYP2A6, CYP2C9; HM: CYP1A1/2, CYP2A6, CYP2B6, Cyp2C8, CYP2C9) a moderate or slight inhibition without dose relationship was demonstrated.

In animal studies for immunotoxicity using Helixor® M in a dose range of 1-10 mg, no evidence was found for immunotoxic effects in terms of absolute numbers for different cellular immune parameters. An increase of leukocytes, B-cells, and an intensified granulopoiesis was observed. In the T-cell dependent immune response, a significantly but only slightly reduced T-cell proliferation was found.

After subcutaneous injection of melanoma cells (B16-F10), the host resistance of the test animals against the tumor was not inhibited by a subsequent treatment with Helixor® at 3 different dosages (0.01, 0.1 and 1 mg Helixor®/kg s.c.).

Data for chronic toxicity, reproductive toxicity and carcinogenicity are not available.

6. Pharmaceutical particulars

6.1 Excipients

Sodium chloride, sodium hydroxide (for adjustment of osmolality and pH-value, respectively). 1 ml Helixor® A/M 1-100 mg contain approximately 3.6 mg sodium. In Helixor® A/M 1 mg to 20 mg: additional water for injection.

6.2 Incompatibilities

In the absence of respective studies, Helixor® should not be mixed with other drugs in the same syringe.

6.3 Shelf live: 3 years

6.4 Special precautions for storage

Keep the ampoules protected from light in the original package; do not store above 30° C.

6.5 Nature and contents of container

Helixor® is available in the following packages: Packs of 6 ampoules of the same strength.

6.6 Special precautions for disposal: No special requirements.

7. Manufacturer

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9. Date of Authorization : 16 May, 2017

10. Date of revision of the text: 05/2017