Iscador® solution for injection

Iscador AG

Anthroposophical medicinal product

Composition
Active substance: fermented aqueous extract of the fresh Viscum album plant from various host trees in a ratio of 1:5, as required with the addition of 0.0002 parts of metal salt as trituration in a potency D4, which, depending on the Iscador Sort (see Table 1), has a content of 10^{-8} g per 100 mg of fresh plant.

Excipients: Aqua ad injectabilia, Natrii chloridum.

Iscador products with the addition "spezifiziert" in the product name differ from the other products by a fixed so-called specified lectin content.

Galenic form and amount active substance per unit
Ampoules of 1 ml solution for injection for subcutaneous injection (s. c.).
The different strengths are designated by the content of fresh plant substance in mg per ml, i.e. per ampoule. For the active substance quantity per unit, see Table 2.

Indications/Applications
In accordance with the anthroposophical understanding of man and nature, Iscador can be used on prescription by your doctor as an additional treatment to improve the quality of life and possibly also the course of the disease in malignant tumor diseases, also with accompanying disorders of the blood-forming organs, in benign tumor diseases and following surgeries on malignant tumors.

Posology/Administration
Selection of the suitable Iscador Sort/host tree see below ("Selection of Iscador Sort").
Subcutaneous injection, if possible near the tumor or metastases, otherwise at constantly changing injection sites (e.g. abdominal skin or thigh, possibly upper arm - not in the case of breast carcinoma). Do not inject into inflamed skin areas or radiation fields. Warm the refrigerated ampoule briefly in the hand.
It is recommended as a precaution not to combine Iscador with other drugs in a syringe (see "Incompatibilities").

The treatment normally comprises two phases:

Induction phase

Unless otherwise prescribed, a gradually increasing dosage with Iscador is recommended at onset of treatment to avoid overreactions with one pack (2× 7 ampoules) Iscador Series 0 from the same host tree. Even after treatment with a different mistletoe preparation, treatment with Iscador must start once again with 2 packs of series 0 of the selected host tree.
1 ml of Iscador is injected subcutaneously 2-3 times a week in increasing strength according to the composition of the series. If series 0 is tolerated well it is permissible to proceed to Iscador Series I or possibly to Series II until the individual reaction dose of the patient is reached or switch to therapy with constant dosage.
The optimal strength or dose must be determined individually. According to the current state of knowledge, the following reactions, which may occur individually or in combination, must be taken into account.

Signs for adequate treatment:

Change in subjective well-being

Improvement of the subjective general condition and pain reduction.

Temperature reaction
Temperature reactions in the form of an above-average increase in body temperature a few hours after injection. In febrile, inflammatory conditions with temperatures above 38 °C (possibly with fatigue, shivering, general feeling of illness, headaches and short-term dizziness), Iscador therapy must not be started until the symptoms have subsided or must be discontinued. Once the symptoms have subsided, the indication for therapy must be re-examined and the treatment then resumed as indicated (see also "Contraindications").

Local inflammatory reaction
Local inflammatory reactions at the injection site up to max. 5 cm diameter. In the case of local reactions over 5 cm in diameter, the next injection should not be administered after these symptoms have subsided and in a reduced strength or dose.
Fatigue, shivering, general malaise, headaches and short-term dizziness on the day of injection are not signs of intolerance, but rather indicate that the dosage is effective and may already be too high. If these symptoms have not subsided by the following day or exceed a tolerable level, the strength or dose should be reduced. In special cases, if the patient does not show any of the above reactions even under the maximum dose of 1 ampoule of 20 mg every other day (or even daily), it is recommended to restart the therapy with Iscador from another host tree with the initiation phase after a therapy break of 1 week.

Maintenance phase

In the maintenance phase, treatment can be carried out in rhythmically changing (Iscador Series) or constant dosage (Iscador Sorts e.g. Iscador spezifiziert). Unless otherwise prescribed, the treatment is continued with the individual strength or dose determined in the induction phase. Treatment is continued either with the Series in which the highest strength has triggered the expected reactions or with the corresponding Sort pack (pack with ampoules of one strength). Series 0 can also be followed by maintenance therapy with Iscador spezifiziert 1 mg. If this is well tolerated, dosage can be increased to 2 mg or 5 mg until the individual reaction dose of the patient on Iscador spezifizert is reached. If indicated based on the individual reactivity (e.g. excessive local reaction) or the course of the disease (e.g. if concomitant immunological tests suggest an increase or a reduction of the dose), either partial amounts of one ampoule or up to 2 ampoules can be injected.

To avoid habituation effects, a rhythmic application is recommended:
-Alternate with smaller strengths or doses in the form of ascending and possibly descending dosage series (only with rhythmic dosage alternation);
-Rhythmization of the injection intervals, e.g. injection on day 1, 2 and 5 of each week;

-insertion of pauses, e.g. 1-2 weeks break after 2× 7 ampoules with rhythmic dosage alternation; if the treatment period is longer, pauses can be extended from the 3rd year of treatment. If the dosage is constant, pauses should only be inserted after the 2nd year of treatment.
If the pause in treatment lasts 4 weeks or longer, a pronounced initial reaction may occur when treatment is resumed. It is therefore recommended to start the treatment with the next lower strength or series, e.g. therapy before pause with Iscador Series II, start after pause with a pack of Iscador Series I, then continue treatment with Series II. In the case of advanced disease or if the patient feels less well on the Iscador-free days, it may be useful to inject 1 ml of Iscador daily without any pause.
The dosage should be checked at intervals of 3-6 months based on the patient's reaction and tumor behavior.

Administration interval
Unless otherwise prescribed: subcutaneous injection 2-3 times a week.

Duration of administration
In principle, the duration of administration is not limited. It is determined individually and depends on the respective risk of recidivation and the individual condition or findings of the patient.

Dosage for children and adolescents
The use of Iscador in pediatric oncology has not been documented sufficiently to demonstrate safety and efficacy in children and adolescents to derive a dosage recommendation.

Dosage in cases of impaired renal function
The available data are insufficient to provide concrete dosage recommendations for patients with impaired renal function. General experience so far has shown no need for dose adjustment.

Selection of Iscador Sort
Based on experience, different preparations are recommended for different localizations of the primary tumor:

Localization of the primary tumor e	Rhythmically changing dosage Induction phase with Series 0, followed by maintenance phase with Series 0, I or II		Constant dosage Induction phase with Series 0, followed by a maintenance phase with Iscador spezifizert or other Sorts
	Recommendation	Alternative	
Gastrointe4stinal tract			
Tongue, oral cavity, esophagus	Qu	M or A	Qu spezifiziert
Stomach, liver, bile, pancreas	Qu c. Cu	M c. Cu	Qu spezifiziert
Small intestine, colon, rectum	Qu c. Hg	M c. Hg	Qu spezifiziert
Anus	P	Qu	P
Urogenital tract			
Kidney	Qu c. Cu	M c. Cu	Qu spezifiziert
Bladder	Qu c. Arg.	A or M c. Arg.	Qu spezifiziert
Prostata, Testis	Qu c. Arg.	A or M c. Arg.	Qu spezifiziert
Penis	P	Qu	P
Uterus, Ovary	M c. Arg.	Qu c. Arg.	M spezifiziert
Vulva, Vagina	M c. Arg.	P c. Hg	M spezifiziert
Cervix	Qu	M	Qu spezifiziert
Mamma			
premenopausal	M c. Arg.	P c. Hg or A	M spezifiziert
perimenopausal	M c. Hg	P c. Hg or A	M spezifiziert

Localization of the primary tumor e	Rhythmically changing dosage Induction phase with Series 0, followed by maintenance phase with Series 0, I or II		Constant dosage Induction phase with Series 0, followed by a maintenance phase with Iscador spezifizert or other Sorts
	Recommendation	Alternative	
postmenopausal (also artificially induced)	P c. Hg	Qu c. Hg	P c. Hg
Respiratory tract			
Nose, pharynx larynx	P Qu	P c. Hg P or A	P Qu spezifiziert
Pleura Bronchi	P U c. Hg	P c. Hg A or Qu c. Hg	P Qu spezifiziert
Endocrinal system			
Thyroid gland	Qu	P	Qu spezifiziert
Skin	P	P c. Hg	P
Sarcomas	P	P c. Hg	P
Brain tumors	P	P c. Hg	P

Contraindications
-In case of known allergy to mistletoe preparations;
-In the case of febrile, inflammatory conditions with temperatures above 38 °C (possibly with fatigue, shivering, general feeling of illness, headaches and short-term dizziness), Iscador therapy must not be started until the symptoms have subsided or must be discontinued. Once the symptoms have subsided, the indication for therapy must be re-examined and the treatment then resumed as indicated;
-in chronic granulomatous diseases, florid autoimmune diseases and those under immunosuppressive treatment;
-in case of hyperthyreosis.
See also "Warnings and precautions" and section "Interactions".

Warnings and precautions
Primary cerebral and spinal cord tumors or intracranial metastases with a risk of cerebral pressure increase: in these cases, the preparations should only be administered after a strict indication and under close clinical control.
See also "Dosage/Application", "Interactions", "Overdose" and "Adverse Effects".

Interactions
There are no studies available on interactions with other substances affecting the immune system. If such preparations are used within the time frame, careful dosage and monitoring of suitable immune parameters are recommended.
Interactions with other medicinal products have not been investigated and have not been described to date.

Pregnancy/lactation
There are few preclinical studies available regarding the effects on pregnancy, birth and postnatal development (see "Preclinical Data"). The potential risk to humans is not known. Iscador should not be used during pregnancy and lactation unless it is clearly indicated.

Effect on ability to drive and use of machines
No such studies have been performed.

Undesirable effects
An increase in body temperature up to febrile level and local inflammatory reactions at the subcutaneous injection site can occur, especially at the beginning of treatment. Slight swelling of regional lymph nodes may also occur.
Localized or systemic allergic or allergoid reactions may occur (usually in the form of generalized itching, urticaria, exanthema or as erythema exsudativum multiforme). In rarely observed general allergic (anaphylactic) reactions following an Iscador injection, with Quincke's oedema, chills, dyspnoea and bronchospasms and shock, immediate emergency antiallergic therapy should be administered and the preparation must discontinued.
Activation of pre-existing inflammation and inflammatory irritation of superficial veins in the injection area is possible. This also necessitates a temporary pause in therapy until the inflammatory reaction subsides.
The occurrence of chronic granulomatous inflammation (sarcoidosis, erythema nodosum) and autoimmune diseases (dermatomyositis) has been reported during mistletoe therapy.
In the case of intracranial and intraspinal tumors, the activation of peritumoral inflammatory processes may occasionally cause intracranial pressure symptoms (headache, visual disturbances, papillooedema, etc.) and require discontinuation of Iscador and anti-edematous therapy.
See also "Warnings and precautions".

Overdose
The symptoms are similar to those of adverse effects (see "Adverse effects") and may require symptomatic therapy. Emergency treatment of an anaphylactic shock is based on the clinical symptoms and consists of all emergency treatment measures.

Properties/Effects
ATC code: L01CX

Mechanism of action/pharmacodynamics
The following could be observed in some of the patients who used Iscador for many years:

-inhibition of tumor growth without affecting healthy tissue;

-increase of the immune and regulatory forces (immune modulation);

-relief of tumor pain;

-improvement of general condition and performance.

Clinical efficacy
In clinical studies, Iscador, as an additive to conventional adjuvant oncological therapy (CAOT), has shown an improvement in subjective general well-being and relief of disease- or therapy-related symptoms such as nausea, vomiting, diarrhoea, fatigue and loss of appetite and subjective pain sensation.

Pharmacokinetics
Studies on pharmacokinetics and bioavailability were not performed for methodological reasons.

Preclinical data

Preclinical studies on acute and sub-acute toxicity show good tolerability in rats and mice. In vitro studies (Ames test, chromosome aberration test) and in vivo studies (micronucleus test) revealed no evidence of mutagenicity. In preclinical *in vivo* studies, no adverse effects were observed following administration of subtoxic doses (in rats and rabbits). Fetal toxicity, ossification delays and skeletal abnormalities were observed in rabbits under Iscador treatment at doses toxic to the mother animals that were 3 times the therapeutic maximum dosage.

Further Remarks

Incompatibilities
As no compatibility studies have been carried out, Iscador must not be mixed with other medicinal products.

Shelf life
The medicinal product may only be used until the date marked "EXP" on the container.
Opened ampoules must not be stored for later injection.

Storage instructions
Store in refrigerator (2-8 °C).
Keep out of reach of children.

Marketing Authorization Number
Iscador M: 56829 (Swissmedic).
Iscador A: 56830 (Swissmedic).
Iscador P: 56831 (Swissmedic).
Iscador U c. Hg: 56832 (Swissmedic).
Iscador Qu: 56833 (Swissmedic).

Packages
Sort packs of 7 ampoules in one strength (see Table 1). (B)
Serial packs as bundle packs with 2× 7 ampoules each in various strength series (see Tables 1 and 3). (B)

Marketing Authorization Holder
Iscador AG, Arlesheim, Switzerland.

Date of information
December 2017.

Iscador assortment/- Individual Sorts/- Serial packs

Iscador assortment

Table 1 Iscador individual sorts and strengths

Host tree	Iscador	Individual sorts acc. strengths									Series bundles (2× 7 ampoules)		
		0,0001 mg	0,001 mg	0,01 mg	0,1 mg	1 mg	2 mg	5 mg	10 mg	20 mg	Series 0	Series I	Series II
Malus (apple tree)	M	X	X	X	X	X			X	X	X	X	X
	M c. Arg.[1]			X	X	X			X	X	X	X	X
	M c. Cu[2]			X	X	X			X	X	X	X	X
	M c. Hg[3]			X	X	X			X	X	X	X	X

Host tree	Iscador	Individual sorts acc. strengths									Series bundles (2× 7 ampoules)		
		0,0001 mg	0,001 mg	0,01 mg	0,1 mg	1 mg	2 mg	5 mg	10 mg	20 mg	Series 0	Series I	Series II
	M spez.[4]					X	X	X					
Quercus (oak)	Qu	X	X	X	X	X			X	X	X	X	X
	Qu c. Arg.[1]			X	X	X			X	X	X	X	X
	Qu c. Cu[2]			X	X	X			X	X	X	X	X
	Qu c. Hg[3]			X	X	X			X	X	X	X	X
	Qu spez.[4]					X	X	X					
Pinus (pine)	P	X	X	X	X	X			X	X	X	X	X
	P c. Hg[3]			X	X	X			X	X	X	X	X
Abies (fir)	A			X	X	X			X	X	X	X	X
Ulmus (elm)	U c. Hg[3]			X	X	X			X	X	X	X	X

[1] as silver carbonate
[2] as copper carbonate
[3] as mercury sulfate
[4] spec = spezifiziert

Table 2 Iscador individual Sorts

Amount of active substance per ampoule	
Iscador strength	Active substance (fermented aqueous extract from the fresh plant substance) in 1 ml solution for injection
20 mg	100 mg (corresponds to 20 mg fresh plant)
10 mg	50 mg (corresponds to 10 mg fresh plant)
1 mg	5 mg (corresponds to 1 mg fresh plant)
0,1 mg	0,5 mg (corresponds to 0,1 mg fresh plant)
0,01 mg	0,05 mg (corresponds to 0,01 mg fresh plant)
0,001 mg	0,005 mg (corresponds to 0,001 mg fresh plant)
0,0001 mg	0,0005 mg (corresponds to 0,0001 mg fresh plant)
spezifiziert 5 mg	25 mg (corresponds to 5 mg fresh plant)
spezifiziert 2 mg	10 mg (corresponds to 2 mg fresh plant)
spezifiziert 1 mg	5 mg (corresponds to 1 mg fresh plant)

Table 3 Iscador Series Packs

Iscador Series	Iscador strength	Number of ampoules per bundle
Series 0	0,01 mg	2× 2
	0,1 mg	2× 2
	1 mg	2× 3
Series I	0,1 mg	2× 2
	1 mg	2× 2
	10 mg	2× 3
Series II	1 mg	2× 2
	10 mg	2× 2
	20 mg	2× 3