

Public Assessment Report

Scientific discussion

Helixor M 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg, 1 mg, solution for injection

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket) has granted Helixor Heilmittel GmbH & Co. KG, Germany, a well-established use approval for the herbal medicinal product Helixor M, 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg, solution for injection. Helixor M is available on prescription and can be bought from pharmacies.

Helixor M 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg is used in individualised palliative cancer care as an adjuvant to conventional therapy. The active ingredient is a liquid water extract from fresh herb of mistletoe grown on apple trees. The approval is based upon data from published scientific literature regarding mistletoe.

The chemical/pharmaceutical quality of the product is acceptable and no serious safety concerns have been identified during the assessment. It was therefore decided that Helixor M, 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg could be approved as a herbal medicinal product.

I. INTRODUCTION

Helixor Heilmittel GmbH & Co. KG, Germany, has applied for a marketing authorisation for Helixor M, 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg, 1 mg, solution for injection. The active substance is *Viscum album* L. ssp. *album* (mistletoe) fresh herb; liquid extract (1:20) 0.09 % NaCl-solution.

The applications for all strengths of Helixor M were submitted under Article 10a Well-established use approval for herbal medicinal products of the Directive 2001/83 EC, as amended.

The assessment reports (i.e. Quality, Clinical and Non-clinical) for Helixor M apply to all strengths of the product (i.e. 100, 50, 30, 20, 10, 5, 1 mg). Furthermore, Helixor M is packed in packages containing ampoules of only one strength as well as packages containing ampoules of different strengths.

For approved indication, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Helixor A are presented in the form of solution for injection containing the active substance *Viscum album* L. ssp. *album* (mistletoe) fresh herb; liquid extract (1:20) 0.09 % NaCl-solution. The strengths 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg corresponds to approximately 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg of fresh herb *Viscum album* L. ssp. *album* growing on *Malus domestica* Borkh. (apple).

The excipients are water, sodium chloride and sodium hydroxide (pH-adjustment). The solution for injection is packed in glass ampoules à 1 ml.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practice, respectively Good Agricultural and Collection Practice).

II.2 Drug Substance

The herbal substance is *Viscum album* L. ssp. *album* growing on *Malus domestica* Borkh.

The harvesting of the mistletoe plant materials is performed over four seasons. Relevant information on growing conditions and controls of the herbal substance (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided. The fresh herb is shredded, diluted, blended and filtrated. The herbal preparation is a mixture of two intermediate extracts to give the final extract Helixor M.

The route of administration is subcutaneous injection, hence water of very high purity (water for injection) was used for the extraction. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

Control of the active substance (herbal preparation) *Viscum album* L. ssp. *album* (mistletoe) fresh herb; liquid extract (1:20) 0.09 % NaCl-solution has been adequately described. Satisfactory specification has been provided.

The active substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

The medicinal product Helixor M is sterile solution for subcutaneous injection. Helixor M, 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg and 1 mg are formulated using excipients described in the current European Pharmacopoeia (Ph. Eur.). All raw materials used in the product are safe with view to possible TSE/BSE risk.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf-life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The long market presence and the high interest in mistletoe products has resulted in a high number of published, peer reviewed, studies on the pharmacology and toxicology of Helixor M as well as other mistletoe products.

III.2 Pharmacology

Mistletoe extract contains a range of substances with potential pharmacodynamic activity, among which mistletoe lectins have been most widely investigated. Besides the lectins, also viscotoxins, phenylpropanoids, phytosterols, triterpenes, saccharides, and polyalcohols may contribute to the pharmacodynamic properties of the extract.

The role of these different compounds is currently not known.

III.3 Pharmacokinetics

Constituents responsible for the therapeutic effect of Helixor M are not entirely known, and thus pharmacokinetic studies are not relevant.

III.4 Toxicology

Local reactions at the site of injection are frequently observed in animal studies.

Studies on reproductive and developmental effects are insufficient.

Published data on genotoxicity and carcinogenicity are not available.

Apart from this, available literature regarding safety pharmacology and toxicity reveals no special hazard for humans.

III.5 Ecotoxicity/environmental risk assessment

Helixor M is a herbal medicinal product. According to “Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SW4447/00), herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.6 Discussion on the non-clinical aspects

A detailed scientific bibliography addressing non-clinical characteristics has been submitted. In accordance with article 10a of Directive 2001/83/EC as amended, for a herbal medicinal product with well established use, the lack of conclusive data on the mechanism of action as well as of pharmacokinetic data is acceptable. The basic requirements for authorisation as a well-established herbal medicinal product from a non-clinical point of view are judged to be fulfilled.

IV. CLINICAL ASPECTS

IV.1 Introduction

The treatment of cancer with mistletoe extracts was first introduced into anthroposophical medicine by Rudolf Steiner around 1920. Mistletoe extract preparations are today the most frequently used complementary and alternative methods (CAM) in the treatment of cancer patients in German-speaking countries.

The Medical Products Agency (MPA) has decided to mainly base the evaluation of clinical efficacy on the review by the Cochrane Collaboration of mistletoe therapy in oncology published in 2008. The review contains assessment of clinical efficacy of mistletoe extracts in general i.e. not of any particular mistletoe extract.

IV.2 Pharmacokinetics

Results from human pharmacokinetic studies with Helixor M or other mistletoe extracts are not available. The total extract is regarded as the active substance, since the role of the individual components of the extract has not been established. Thus the lack of pharmacokinetic studies is acceptable.

IV.3 Pharmacodynamics

The mechanism of action has not been clarified.

IV.4 Clinical efficacy

A Cochrane review concerning mistletoe therapy in oncology was published in 2008 (Horneber M, et al). It is a joint assessment of different mistletoe extracts, dosage and treatment duration. The objective of the review was to determine the effectiveness, tolerability and safety of mistletoe extracts given either as monotherapy or adjunct therapy, i.e. given concomitantly with chemo- or radiotherapy, for patients with cancer.

The outcome measures assessed were survival time, tumour response, quality of life (QoL), psychological distress, adverse effects from antineoplastic treatment and safety of mistletoe extracts.

In the studies evaluated, 3484 cancer patients were included and randomised. In five studies Helixor with varying dosage was used. The number of patients withdrawing or dropping out was reported for all of the studies included in the Cochrane review.

In conclusion, the study results are seen as insufficient to provide clear guidelines for the use of mistletoe extracts in oncological practice. There is some support as regards health-related QoL. There is no clear evidence for superiority of one preparation or treatment schedule over the other.

Eight clinical studies were listed in the Cochrane review as studies to be assessed in an upcoming update of the review. An assessment of these studies has been performed by the MPA. None of these studies is judged to be of pivotal importance.

IV.5 Clinical safety

The MPA agrees with the Cochrane assessors and the applicant that mistletoe extracts are usually well tolerated and have only few side effects. This is supported by the longstanding and wide-spread use of mistletoe extracts in cancer therapy, especially in some European countries.

Twelve studies included in the Cochrane review reported on adverse effects related to treatment with mistletoe extracts. The local reactions most commonly reported were redness, itching and induration at the injection site, appearing in up to one third of the patients. Among systemic reactions, mild fever and flu-like symptoms were reported in 10% of the patients. Adverse reactions known to be caused by mistletoe extract preparations, including anaphylactic reactions, are formerly known to the MPA. No new safety issues have been identified during the assessment procedure.

IV.6 Discussion on the clinical aspects

In the opinion of the MPA, due to longstanding and widespread use of mistletoe products in cancer treatment in the European Union, mistletoe extract products should be available for Swedish cancer patients in individualised palliative cancer care as an adjuvant to conventional therapy.

Based on the proposed posology, there is insufficient evidence in support of tumour response, delay in tumour progression and concerning survival benefit.

No studies of drug-drug interactions have been performed. As a precautionary measure, a contraindication to concomitant treatment with immunomodulators (with the exception of cytotoxic drugs) and immunostimulants is advised.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has shown that the chemical/pharmaceutical quality is acceptable and can confirm that the process is under control and ensure both batch reproducibility and compliance with the product specification.

The adverse reactions reported during an extensive use of mistletoe products are no cause for safety concern. No new safety signals have been identified in the submitted documentation.

The benefit/risk ratio is considered positive and Helixor M, solution for injection, is recommended for approval.

VI. APPROVAL

Helixor M, 100 mg, 50 mg, 30 mg, 20 mg, 10 mg, 5 mg, 1 mg, solution for injection was approved in the national procedure on 2013-12-06.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)