

Public Assessment Report

Scientific discussion

Prospan, oral solution in single-dose container
(*Hedera helix* L. folium; dry extract (DER 5-7.5:1); ethanol 30%)

Asp. no: 2010-0149

This module reflects the scientific discussion for the approval of Prospan, oral solution in single-dose container. The procedure was finalised 24 June 2010. For information on changes after this date please refer to the module 'Update'.

LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Engelhard Arzneimittel GmbH & Co KG a marketing authorisation for the herbal medicinal product Prospan, oral solution in single-dose container. The product is available without prescription and can be bought from pharmacies and other outlets.

Prospan has an extensive medicinal use in the EU as an expectorant in case of productive cough. The active ingredient is a dry extract (ethanol 30 %) of dried leaves of *Hedera helix*. The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has concluded that the active substance in Prospan has a well-established medicinal use with a recognised efficacy and an acceptable level of safety.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Prospan could be granted a marketing authorisation as a herbal medicinal product.

I. INTRODUCTION

Engelhard Arzneimittel GmbH & Co KG, Germany, has applied for a marketing authorisation for Prospan, oral solution in single-dose container. The active substance is a dry extract from the dried leaves of *Hedera helix* L. (ivy/murgröna).

For approved indications, see the Summary of Product Characteristics (SmPC).

Prospan, oral solution in single-dose container was first authorised as a natural remedy in 2009, as a new pharmaceutical form of the already authorised Prospan, oral solution. As a consequence of the new legislation regarding (traditional) herbal medicinal products the product was reclassified as a herbal medicinal product in 2010.

II. QUALITY ASPECTS

II.1 Introduction

Prospan is presented in the form of an oral solution containing 7 mg of genuine extract per ml (35 mg per single-dose container), which corresponds to approximately 44 mg/ml (220 mg per single-dose container) of dried leaves from *Hedera helix*.

The excipients are: water, sorbitol, xanthan gum, potassium sorbate, orange flavour, anhydrous citric acid, Frescofort Flavour Permaseal (maltodextrin, peppermint flavour, maize starch) and levomenthol.

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

Herbal substance: *Hedera helix* L., dried leaves.

A monograph is available in the European Pharmacopoeia (Ph. Eur.).

Herbal preparation (active substance): *Hedera helix* L. dried leaf, dry extract (5-7.5:1), ethanol 30 %.

The herbal substance is collected from the wild. Relevant information on growing conditions and controls of the herbal substance has been provided.

The herbal substance is dried, cut and extracted with 30 % ethanol. The resulting extract is concentrated to the dry extract which is regarded as the active substance. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The specifications for both the herbal substance and the herbal preparation include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted.

II.3 Medicinal Product

Prospan, oral solution in single-dose container is formulated using excipients described in the current European Pharmacopoeia (Ph. Eur.), except for orange flavour and Frescofort Flavour Permaseal which are controlled by in-house monographs. 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 and storage conditions claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Hedera helix* L., folium, in 2011. In this monograph, it was concluded that the active substance in Prospan (dry extract (ethanol 30 %) from *Hedera helix* leaf) has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

III.2 Pharmacology

In the HMPC assessment report on *Hedera helix* L., folium, an extensive summary of experimental findings on pharmacology is included.

A spasmolytic/bronchodilating effect has been documented in *in-vitro* experiments and in *in-vivo* studies in guinea pigs. The mechanism of the secretolytic activity observed in clinical praxis is not yet clarified in experiments. Anti-inflammatory effects could be shown in different *in-vivo* models, for example with orally administered ethanolic *Hedera helix* leaf extract. Antibacterial activity of saponins from *Hedera helix* against a large number of microorganisms was shown *in-vitro*. Antiviral activity of hederacoside C was demonstrated in *in-vitro* experiments with the influenza virus.

In summary, the pharmacological data of different *in-vitro* and *in-vivo* experiments, conducted with *Hedera helix* leaves extract or saponins, support the use of ivy preparations in the context of inflammatory bronchial diseases and cough and colds.

III.3 Pharmacokinetics

Constituents responsible for the therapeutic effect of the extract are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

III.4 Toxicology

Single and repeated dose toxicity studies have been performed using dry extract from *Hedera helix* leaf. The results did not raise any safety concern.

The extract from *Hedera helix* leaf was not considered mutagenic, neither in *in-vitro* nor in *in-vivo* studies.

The inactive ingredients in Prospan are common pharmaceutical and/or food ingredients and are not considered to pose any risk.

III.5 Ecotoxicity/environmental risk assessment

Prospan 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 Conclusion on the non-clinical aspects

The information supplied supports medicinal use of the product. No serious safety concerns have been identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Hedera helix* in 2011. In this monograph, it was concluded that the active substance in Prospan (dry extract (ethanol 30 %) from *Hedera helix* leaf) has a well-established medicinal use as an expectorant in case of productive cough and an acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

IV.2 Pharmacokinetics

There are no pharmacokinetic studies concerning the extract in Prospan. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of hydroalcoholic extract of *Hedera helix* are not entirely known, and thus pharmacokinetic studies are not possible/ relevant.

IV.3 Pharmacodynamics

The mechanism of therapeutic action cannot be considered clarified at present. The entire extract is regarded as being the active constituent of Prospan.

IV.4 Clinical efficacy

In the assessment report pertaining to the Community monograph on *Hedera helix*, an extensive review of clinical trials on all types of *Hedera helix* extracts and diseases of the respiratory tract was presented.

A randomized controlled double-blind comparative study showed that ivy extracts could be therapeutically equivalent to the secrolytic drug ambroxol in improvement of symptoms of cough in adults with chronic bronchitis. The study results indicate that patients with simple chronic bronchitis and patients with obstructive chronic bronchitis may benefit from the ivy preparation for decreases in frequency of coughing, sputum production and dyspnoea, comparable to the secrolytic therapy with ambroxol. The benefit is shown only for short term use of maximum 4 weeks.

Two other studies (open and controlled) in children with acute inflammatory diseases of the respiratory tract/acute bronchitis comparing Prospan with either ambroxol or acetylcysteine support the results from the study above, referring to the secrolytic activity.

These study results are pivotal for the well-established use indication "Herbal medicinal product used as an expectorant in case of productive cough" although data from numerous other clinical trials also support this indication.

IV.5 Clinical safety

A large number of patients, children as well as adults, have been exposed to Prospan in clinical trials but above all through extensive sales of the product in the European Union. The clinical safety documentation as well as the non-clinical safety documentation indicates a low toxicity and absence of serious adverse events of the product. In addition, Periodic Safety Update Reports (PSUR) for Prospan as a natural remedy support this conclusion. Adverse reactions reported are gastro-intestinal disorders (nausea, vomiting, diarrhoea) and allergic reactions (urticaria, skin rash, dyspnoea). These adverse events are included in the the SmPC.

Due to the lack of safety data, the use of products containing *Hedera helix* leaf during pregnancy and lactation is not recommended.

The use in children under 2 years of age is contraindicated because of the risk of aggravation of respiratory symptoms. Prospan, oral solution in single-dose container is not recommended for use in children between 2 and 6 years of age due to lack of adequate data for the specific dose in this age category.

For special warnings and precautions for use see the SmPC.

In conclusion, no new signals of safety concern have been identified.

IV.6 Discussion on the clinical aspects

Prospan is a herbal medicinal product available without prescription as an expectorant in case of productive cough.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

According to the Community monograph on *Hedera helix*, folium, the extract in Prospan has a well-established medicinal use with a recognised efficacy and an acceptable level of safety used as an expectorant in case of productive cough.

The adverse reactions reported during an extensive use of *Hedera helix* are no cause for safety concern. No new safety signals have been identified in the submitted product specific documentation relating to Prospan.

The benefit/risk ratio is considered positive and Prospan, oral solution in single-dose container is recommended for approval.

VI. APPROVAL

Prospan, oral solution in single-dose container was approved in the national procedure on 2010-06-24.

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)