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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Arkovox Syrup

IVY LEAF DRY EXTRACT (HEDERA HELIX L.) (4-6:1) EXTRACTION SOLVENT: ETHANOL 30% V/V
PA1450/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Arkovox syrup from Laboratoires Arkopharma on 10th January 2013 for productive cough.

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC and is referred to as an "well established use" application for a herbal product.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product	Arkovox Syrup
Name(s) of the active substance(s) (INN)	Ivy Leaf *(Hedera helix* L.*)* dry extract (4-6:1) Extraction solvent: ethanol 30% v/v
Pharmacotherapeutic classification (ATC code)	R05 Cough & Cold Preparations
Pharmaceutical form and strength(s)	Syrup
Marketing Authorisation Number(s) in Ireland (PA)	PA1450/1/1
Marketing Authorisation Holder	Laboratoires Arkopharma

II QUALITY ASPECTS

II.1. Introduction

This application is for Arkovox syrup.

II.2 Drug substance

The active substance is a dry extract from Ivy Leaf *(Hedera helix* L.*)* and is an established active substance manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Arkovox is a brown syrup.

Each 5 ml of syrup contains 50 m g of Ivy Leaf (*Hedera helix* L.) dry extract (DER 4-6:1), extraction solvent ethanol 30% (v/v).

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably

qualified manufacturing sites.

The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is adequate and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in brown polyethylene bottles of 100 ml, 150 ml or 200 ml with white polyethylene caps and a graduated measuring spoon.

Evidence has been provided that the packaging materials comply with Ph. Eur. and with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years with no special storage requirements. The product should be used within 3 months of opening.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Arkovox syrup.

III NON-CLINICAL ASPECTS

III.1 Introduction

Compliance with GPL, suggested text:
The IMB has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

The mechanism of action of ivy leaf extracts as expectorants is not fully understood. Expectorant action through secretolytic activity via vagal stimulation has been proposed.

III.3 Pharmacokinetics

No pharmacokinetic data in humans is available.

III.4 Toxicology

The main constituents of ivy leaf are triterpene saponins (2.5-6%), predominantly bisdesmosidic glycosides of hederagenin with hederasaponin C (hederacoside C) as the main saponin, and a small amount of the monodesmosidic saponin α-hederin. Other saponins, in decreasing order of concentration, are hederasaponins B, D, F, G, E, H and I. Other constituents include phytosterols, polyines such as falcarinol and didehydrofalcarinol, essential oil, flavonoids and other phenolic compounds such as caffeoylquinic acids.

The applicant has presented a summary of toxicity studies mainly from the literature, including acute and repeat dose toxicity, genotoxicity, reproductive and developmental toxicity. No carcinogenicity studies are available. Information provided in the EMA assessment report on Hedera helix L., folium. suggests that the in general the quality of toxicity studies is limited.

Based on the repeat dose toxicity results it can be concluded that there is a high safety margin between the No Observed Effect Level (NOEL) for ivy syrup as assessed by the oral route in rats and the recommended daily dose in children and adults.

Embryotoxic effects were observed in rats following subcutaneous administration (single and repeated). No studies were conducted on the effect of an oral preparation.In view of this finding ivy leaf syrup is not recommended in preganancy or lactation.

Haemolytic effects in rats were only observed following exposures in excess of maximum human exposure.

Regarding mutagenicity studies, α-Hederin, ß-hederin and δ-hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using *Salmonella typhimurium* strain TA 98, with or without S9 activation.

III.5 Ecotoxicity/environmental risk assessment

Not required

III.6 Discussion on the non-clinical aspects

Extracts of ivy leaves are used therapeutically in commercially available preparations in Europe for the treatment at common cold associated with cough and symptomatic treatment of acute and chronic inflammatory bronchial disorders. Single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies do not exist according to the state of the art and the relevant guidelines. The limited toxicity data available suggest a risk of embryotoxicty as well as a haemolytic effect in rats at exposures in excess of the maximum human exposure. Given the risk of embryotoxicity and the lack of data in pregnant humans, ivy leaf syrup is not recommended during pregancny or lactation.

IV CLINICAL ASPECTS

IV.1 Introduction

Hedera helix L has been granted a community herbal monograph for well established use and for traditional use. Ivy syrup consists of a syrup containing solely of one active ingredient: a quantified ivy leaf dry extract (DER 4-6:1), extraction solvent ethanol 30% (V/V) [100 ml syrup contains 1.00 g dry extract]. The applicant claims essential similarity with an ivy leaf product Prospan which has a DER (5-7.5:1) which is included in the monograph under herbal preparations type (a) –Dry extract (DER 4-8:1), extraction solvent ethanol 24-30% m/m.

The indication sought for this product is that of an expectorant in the case of a productive cough.

IV.2 Pharmacokinetics

No data is available on pharmacokinetics

IV.3 Pharmacodynamics

No data is available on pharmacodynamics

IV.4 Clinical Efficacy

As this is a herbal application submitted under well established use there is limited data on clinical efficacy. The applicant has submitted a detailed clinical overview as well as a summary of efficacy. The information provided in these documents appears to come mainly from the assessment report on Hedera helix of the Committee of Herbal Medicine Products (HMPC). Studies assessed in the Committee of Herbal Medicinal Products assessment report on Hedera helix L folium were mainly observational studies. The level of evidence provided by such studies tends to be low. The report concluded that the benefit risk for Hedera helix was positive.

A systematic review of clinical trials assessing the effectiveness of Ivy Leaf included 10 studies, only three of which were controlled trials and of these only one was a good quality randomised controlled trial. They concluded that the combination of ivy and thyme might be effective in the treatment of acute respiratory tract infections. Whilst all of the trials included in the review concluded that ivy extracts are effective in reducing URTI symptoms, in general these trials were of poor quality. (Holzinger F, Chenot Jean Francois. Systematic Review of Clinical Trials Assessing the Effectiveness of Ivy Leaf (Hedera Helix) for Acute Upper Respiratory Tract Infections. Evidence based Complementary and Alternative Medicine Volume 2011 (2011), Article ID 382789,9 pages. doi:10.1155/2011/382789)

IV.5 Clinical Safety

Data on safety has been provided in the safety summary and most of this appears to have been taken from the HMPC assessment report. This data is taken from uncontrolled and controlled studies of Hedera helix.

Ivy preparations have been marketed worldwide in many countries in large quantities. More than 10,000 patients have been included in open multicenter prospective surveillance studies with a high dosage range. Approximately 7,000 children were included in prospective clinical studies. A retrospective study was conducted with about 52,000 children.

The monograph has highlighted gastrointestinal effects (e.g. nausea, vomiting and diarrhoea) as occurring with a frequency of common and allergic reactions (urticaria, skin rash, couperoses and dyspnoea) as occurring with a frequency of uncommon. In a study which included more than 5000 children gastrointestinal reactions were noted in 1.5% and allergic reactions in 0.1% (Fazio et al 2006) .

Deaths
One death was reported in a 3 year old boy who was found dead. He appeared to have aspirated vomit. He had taken codeine juice, ibuprofen juice, and Prospan drops (Hedera helix). Information on the dosage and formulation of the ivy product was unclear. Post mortem analysis showed high concentrations of codeine and morphine.
The causal relationship to codeine, according the physician´s comment, was probable. An interaction with the ivy preparation is theoretically also possible. This potential interaction is addressed in section 4.4 of the SmPC which advises that Ivy leaf syrup should not be used with antitussives such as codeine or dextromethorphane.

Serious adverse events
These have not been described as a category in the HMPC assessment report. The safety overview states that no serious adverse events have been reported.

Drug interactions
There is limited data on drug interactions. Two adverse events were reported in children following administration of narcotics and ivy leave preparations.

Safety studies in children
Approximately 7000 children were included in prospective studies and 52,000 children in a retrospective study.
In a prospective study by Fazio (2000) 5,181 children were treated with Prospan cough juice. Adverse events were reported in 1.2% of the children. Forty six (0.5%) patients discontinued therapy due to adverse events, mainly gastrointestinal disorders. The main adverse events were: gastrointestinal disorders 1.5% (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%), skin allergy 0.1%. Other adverse events occurring with a frequency of less than 0.1% were: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache, drowsiness.

A retrospective study by Kraft (2004) showed that the most frequent adverse events were: diarrhoea (0.1%), enteritis (0.04%), allergic exanthema/urticaria (0.04%) and vomiting (0.02%). In total, gastrointestinal disturbances occurred in 0.17% of the children. The incidence of adverse effects was age dependent. In children under 1 year, adverse effects occurred in 0.4% and in children up to 9 years in 0.13%.

Hypersensitivity reactions

Allergic contact dermatitis following contact of the skin with ivy is well known. Skin allergy has been reported in 0.1% of the population in the Fazio study and allergic exanthema/urticaria in 0/04% of those in the retrospective Kraft study. There are 63 case reports in the BfArM Database on suspected adverse drug reactions (October 2009). Most of them are related to allergic reactions (urticaria, skin rash, tuberose, dyspnoea) and gastrointestinal reactions (nausea, vomiting and diarrhoea).

Given the potential seriousness of dyspnoea as an adverse event further information on reported cases of dyspnoea was sought from the applicant.

- how many cases of dyspnoea had been reported to BfArM?
- had there been case reports of dyspnoea to other regulatory agencies?
- was the dyspnoea severe?
- in what proportion of reported cases was the dyspnoea severe,
- did those experiencing dyspnoea require any treatment for their dyspnoea?

Five cases of dyspnoea associated with the use of Hedera helix were found on searching the public data available on the BfArM database. These cases were reported between 1995 and 2013. One of the reported cases was a male aged between 0 and 4 years, the remaining cases were adults. In three cases dyspnoea was associated with other allergic reactions e.g. allergic dermatitis and pruritis, hypersensitivity and enlarged uvula. In two cases Ivy leaf preparations had been taken with other medicines and in the third case the medicinal product was a combined ivy leaf and thyme preparation. The severity of the dyspnoea was not indicated. None of the 5 experienced death and recovery was observed in all cases. In all cases Ivy leaf preparations were believed to have a ‘suspected’ relationship with dyspnoea.

PSUR reports for Arkovox

A total of 300,000 units of Arkovox have been sold in France between 2001 (when it was first authorized) and 2009. In that time there have been no reports of adverse events to the applicant. In addition no adverse events have been notified between 2009 and to date.

Conclusions on safety

The most frequently reported adverse events are gastrointestinal in nature with a frequency of common. The second most frequent adverse events are allergic reactions with a frequency of uncommon. The frequency of allergic reactions has not been presented by type of reaction. The applicant was asked to further investigate reports of dyspnoea an allergic reaction at the more serious end of the spectrum. Public data available from the German regulatory agency BfArM was interrogated. Five cases of dyspnoea were identified over a period of 18 years. The information on each case is limited. All were believed to have a suspected relationship between an Ivy leaf preparation and dyspnoea.

Given the widespread use of Ivy leaf cough products in Germany and the fact that 5 cases of dyspnoea were reported over an 18 year period the frequency of a dyspnoea as an adverse event is likely to be very low.

No serious adverse events were described in the HMPC report and safety review submitted by the applicant stated that no serious adverse events had been reported.

One death was was reported in a 3 year old boy who was found dead. He appeared to have aspirated vomit. He had taken codeine juice, ibuprofen juice, and Prospan drops (Hedera helix). Information on the dosage and formulation of the ivy product was unclear. It was concluded that there was a probable relationship between codeine and death but a possible relationship with the ivy leaf product could not be ruled out. This potential interaction is addressed in section 4.4 of the SmPC.

Overall ivy leaf cough preparations appear to be safe.

Risk Management Plan

As this application was submitted prior to July 2012 a Risk Managment Plan is not required.

This well established use application has been submitted in accordance with Article 10a of Directive 2001/83/EC and

so therefore the requirement for periodic safety update report (PSUR) submissions is waived.

The Marketing Authorisation Holder (MAH) submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the European Union or from a Third Country.

SmPC and PIL
The applicant was asked to bring the posology in section 4.2 of the proposed SmPC in line with the range proposed in the well established use monograph for ivy leaf extract (DER 4-8:1) extraction solvent ethanol 24-30% m/m. In addition the applicant was asked to simplify the language of the patient information leaflet (PL), to describe the frequency of adverse events and to provide a PL in the quality review of documents (QRD) format.

IV.6 Discussion on the clinical aspects

As this is an herbal application submitted under well established use there is limited data on clinical efficacy. The applicant has submitted a detailed clinical overview as well as a summary of efficacy. The information provided in these documents appears to come mainly from the assessment report on Hedera helix of the Committee of Herbal Medicine Products (HMPC). Studies assessed in the Committee of Herbal Medicinal Products assessment report on Hedera helix L folium were mainly observational studies. The level of evidence provided by such studies tends to be low. The report concluded that the benefit risk for Hedera helix was positive.

Ivy leaf preparations have been marketed worldwide in large quantities. The most frequently reported adverse events are gastrointestinal in nature with a frequency of common. There have been 5 reports of dyspnoea reported to BfArM over an 18 year period. All patients recovered. Of the five, one was a child. Given the widespread use of Ivy leaf cough products in Germany the frequency of a dyspnoea as an adverse event is likely to be very low.
Overall the product appears to be safe.

V OVERALL CONCLUSIONS

This is a well established use application for an herbal product Arkovox.
Ivy leaf preparations have been reviewed by the HMPC and it has been concluded that the benefit risk assessment for Arkovox is positive for use as an expectorant in the case of productive cough.

The submitted SmPC and PL is broadly in line with the monograph agreed for Dry extract (DER 4-8:1), extraction solvent (well established use) ethanol 24-30% m/m.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.