LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Laif, Film-coated tablet
[*Hypericum perforatum* L. (St. John's wort) dry extract]

Asp. no: 2009-0137

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I. INTRODUCTION

Green Medicine AB, Malmö, Sweden, has applied for a marketing authorisation for Laif, film-coated tablets. The active substance is a dry extract (ethanol 80 %) from St. John's wort (*Hypericum perforatum* L.). For approved indication, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Laif is presented in the form of film-coated tablets containing 900 mg of St. John's wort, dry extract which corresponds approximately to 4 g of St. John's wort. The excipients are Colloidal anhydrous silica, Talc, Titanium dioxide, Sodium hydrogen carbonate, Sodium starch glycolate (type A), Croscarmellose sodium, Magnesium stearate, Poly[butylmethacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methylmethacrylate] (1:2:1) (Eudragit E 100), Macrogol 4000 and
Riboflavin (E 101).
The capsules are packed in blisters (PVC/PVDC/Al).

II.2 Drug Substance

The active substance (herbal preparation), St. John's Wort Dry Extract, Quantified has a monograph in the Ph Eur and so has the herbal substance St. John's Wort.

St. John's Wort Dry Extract, Quantified is a brownish-grey powder. Relevant information on growing conditions and controls of the herbal substance have been provided. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The active substance specification includes 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 and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Laif, film-coated tablets is formulated using excipients described in the current Ph Eur, All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

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 Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Hypericum perforatum* in 2009. In this monograph, it was concluded that the active substance in Laif [dry extract (ethanol 80 %) from *Hypericum perforatum*] 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

A series of bioactive compounds has been detected in *Hypericum*, namely phenylpropanes, flavonol derivatives, biflavones, proanthocyanidins, xanthones, phloroglucinols, some amino acids, naphthodianthrones and essential oil constituents. In the recent past, the antidepressant activity of *Hypericum* extracts has been variously attributed to the phloroglucinol derivative hyperforin, to the naphthodianthrones hypericin and pseudohypericin and to several flavonoids. The role of these different compounds is still a matter of debate. It is likely that multiple bioactive compounds contribute to the antidepressant activity of the crude plant extract in a complex manner.

III.3 Pharmacokinetics

Constituents responsible for the therapeutic effect of hydroalcoholic extract of *Hypericum* are not entirely known, and thus pharmacokinetic studies are not possible/ relevant.

III.4 Toxicology

No signals of safety concern were identified in experimental studies of single dose toxicity, repeat dose toxicity, genotoxicity, or reproductive and developmental toxicity. Complete studies on carcinogenicity have not been performed, but long term experiments over a period of 52 weeks in rats and dogs did not show any evidence of

tumorigenicity. Based on available toxicological and clinical experience there are no grounds for suspicion of a carcinogenic effect.

III.5 Ecotoxicity/environmental risk assessment

Laif is an herbal medicinal product. According to “Guideline on the environmental risk assessment of medicinal products for human use (EMEA/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

Hypericum perforatum extracts have been in medicinal use in the Community for a long period of time. The dry extract in Laif is recognised to have a well established medicinal use with an acceptable level of safety in the European Community. However, isolated hypericin seems to have teratogenic properties. For safety reasons the oral use of *Hypericum* during pregnancy and lactation should not be recommended. (Community monograph, 2009).

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 *Hypericum perforatum* in 2009. In this monograph, it was concluded that the active substance in Laif [dry extract (ethanol 80 %) from *Hypericum perforatum*] 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.
According to the Community monograph, the extract in Laif has a well-established medicinal use in the treatment of mild to moderate depressive episodes (ICD-10).The reader is referred to the Community monograph and the pertinent assessment report for details.

IV.2 Pharmacokinetics

Pharmacokinetic data on marker substances in *Hypericum* extract are available. They are, however, of very limited therapeutic usefulness, as a clear relationship with a therapeutic effect of these compounds has not been established. The total extract is consequently seen as the active substance.

IV.3 Pharmacodynamics

At present, it is not possible to designate a particular substance to the antidepressant activity with certainty. The mechanism of therapeutic action cannot be considered

clarified. It appears likely that the overall effect of *Hypericum* extract depends on several substances and mechanisms.

IV.4 Clinical efficacy

In the assessment report pertaining to the Community monograph on *Hypericum perforatum*, an extensive review of clinical trials on all types of *Hypericum* extracts was presented. The assessment report included information from the latest Cochrane review by Linde (2008), who assessed the outcome of studies in which exclusively patients with major depression were treated. 29 trials (5489 patients) including 18 comparisons with placebo and 17 comparisons with standard antidepressants met the inclusion criteria; the duration of treatment was 4-12 weeks. Overall the *Hypericum* treatment was superior to placebo and similarly effective as standard antidepressants.

Sufficient clinical data were available in the public domain to include the extract in Laif in the Community monograph on *Hypericum perforatum*, herba with the indication 'Herbal medicinal product for the treatment of mild to moderate depressive episodes (ICD-10)'. The product specific studies on Laif submitted in this application were included in the studies assessed for the Community monograph.

IV.5 Clinical safety

In the assessment report pertaining to the Community monograph on *Hypericum perforatum*, the adverse events observed in clinical trials of Hypericum extracts were stated to have been generally mild and the frequency considerably lower than that observed for standard antidepressants.
Hypericum extracts induce the activity of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein. Concomitant use of Laif and drugs metabolised by these enzymes will lead to pharmacokinetic interactions. Particularly the induction of CYP3A4 is well documented and the degree of induction is directly correlated to the amount of hyperforin in the herbal preparation.

There were no new signals of safety concern in the submitted product specific documentation relating to Laif. It is known that gastrointestinal disorders, allergic skin reactions, fatigue and restlessness may occur and that fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight. These adverse effects do not appear to be very common, but actual frequency figures are lacking.

IV.6 Discussion on the clinical aspects

Mild to moderate depressive episodes (major depressive episodes) are serious conditions that are often recurrent and linked to an increased morbidity and mortality. The patient is required to see a doctor for diagnosis and should be closely monitored during treatment. It is not a condition that is suitable for self-medication. The combination of this increased mortality risk due to the underlying disease and the

obvious risk of interactions with other medication lead to the conclusion that Laif must be subject to medical prescription.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

According to the Community monograph, the extract in Laif has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the treatment of mild to moderate depressive episodes. Overall, the available clinical data indicate that Laif is superior to placebo and similarly effective to standard antidepressants in the treatment of mild to moderate major depressive episodes.
The clinical safety data available for Laif indicates that the frequency and severity of adverse effects are lower than those of standard antidepressants. This finding is also supported by the results extracted from the literature on clinical trials of other *Hypericum* products.
The major safety issue with Laif is the kinetic interaction with other drug substances metabolised by the liver. However, the mechanism of the interaction is well-known today, and the problem can be handled by a careful exclusion of patients using other important medication metabolised by CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein.
Given that the problem of interactions is appropriately addressed in the SPC, and that the product is subject to medical prescription, the benefits of Laif should outweigh the potential risks.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was German.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Laif, film-coated tablets is recommended for approval.

VI. APPROVAL

Laif, film-coated tablets was approved in the national procedure on 2012-02-24.

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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)

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