"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו"
Physicians Prescribing Information

Laif®600

Film-Coated Tablets

The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health on 01/2015

NAME OF THE MEDICINAL PRODUCT: LAIF® 600

Qualitative and quantitative composition:
1 film-coated tablet contains the following active ingredient: Dry Extract of St. John's Wort (5 - 8:1) 612.0 mg ; Extracting agent: 50 vol.-% ethanol (v/v)

St. John's Wort is also called Hyperici Herba Extractum Siccum and Hypericum Perforatum.

For other ingredients, see section **List of excipients.**

Pharmaceutical form:
Film-coated tablet (for oral administration)

CLINICAL PARTICULARS
Therapeutic indications: Symptoms of mild to moderate depression. Treatment is recommended for up to 24 weeks.

Posology, mode and duration of administration:
Unless otherwise prescribed, adults and juveniles aged 12 and above, take 1 film-coated tablet once daily, swallowed whole together with some liquid after breakfast.
Since the effect of the medicine builds up gradually, LAIF® 600 should be taken consistently.

LAIF® 600 has been proven effective in comparison to Sertraline in clinical studies conducted up to 24 weeks.

LAIF® 600 may be prescribed for a period longer than 24 weeks, following the physician's assessment of the benefit-safety profile in long-term use.

Experience has shown that administration for 4 to 6 weeks is necessary to achieve noticeable symptom relief. The patient information leaflet states that in case of symptoms persisting over a period exceeding 4 weeks, or if symptoms should become worse despite proper dosage, a physician must be seen.

Contraindications: LAIF® 600 may not be taken concomitantly with medicines, which contain the following active ingredients or contain an active ingredient from the following substance groups:
- Immunsuppressants: Cyclosporine, tacrolimus for internal application, sirolimus.
- Antiretroviral medications: Indinavir, nevirapin.
- Cytostatic agents: Imatinib, irinotecan.

LAIF® 600 may not be taken concomitantly with other antidepressants.
LAIF® 600 may not be taken in cases of known allergy to St. John's Wort or to one of the excipients.
The use in children under 12 years of age is not recommended.

Special warnings and special precautions for use:
Concomitant administration of LAIF® 600 and one of the active substances listed under "Interactions with other medicines and other agents" can lead to diminished or enhanced effect of these medicines. Patients, who are taking one of these active substances, should be possibly monitored (laboratory values).

Intense UV irradiation (sunbathing, sunlamp, solarium) should be avoided during administration of LAIF® 600.
The patient is advised in the package insert that they should inform their physician if they are taking LAIF® 600 and have been prescribed a further medicine. If the patients wish to take a further medicine themselves, they should heed the instructions in the section "Interactions with other medicines and other agents".

LAIF® 600 contains lactose. Patients with rare hereditary problem of galactose intolerance, lac-tase deficiency or glucose-galactose malabsorption should not take LAIF® 600.

Interactions with other medicinal products and other interactions:
Medicines, containing active substances of St. John's wort like LAIF® 600 does, may possibly interact with other medicinal substances. Active constituents of St. John's Wort can cause accelerated excretion of other medicinal substances and thereby reduce the efficacy of these other substances. Active constituents of St. John's Wort, administered together with other medicines, can raise also the concentration of transmitters (e.g. serotonin).

LAIF® 600 can interact with the following active substances and thereby diminish the effect of these active substances:
- Immunsuppressants: Cyclosporine, tacrolimus for internal application, sirolimus.
- Antiretroviral medications: Indinavir, nevirapin.
- Cytostatic agents: Imatinib, Irinotecan.
- Anticoagulants such as phenprocoumon, warfarin, Rivaroxaban.
- Digoxin, midazolam, simvastatin, ivabradine, verapamil, hormonal contraceptives.
- Tricyclic antidepressants such as amitriptyline, nortriptyline.
- monoamine oxidase (MAO) inhibitors such as rasagiline for the treatment of Parkinson disease.

Drug interactions leading to enhanced effect are possible when LAIF® 600 is taken concomitantly with certain antidepressants such as paroxetine, sertraline and trazodone. Concomitant intake of these medicines can result in increasing occurrence of serotoninergic effects (e.g. nausea, vomiting, anxiety, restlessness and confusion) in isolated cases. In woman taking hormonal contraceptives ("The pill") concomitantly with LAIF® 600, Intermenstrual bleeding (spotting) may occur, and the contraceptive reliability of "the pill" may be diminished. Therefore, the patient information leaflet advises that additional contraceptives measures should be taken.

Further interactions with medicines, which are metabolized via the cytochrome P 450 enzyme system in the liver, are possible.

Pregnancy and the lactation period:
The patient information leaflet advises that due to the high interaction potential of this medicinal product pregnant and breast-feeding women should only take this medicinal product after consulting with their physician first. Specific data for pregnancy and lactation is not available

Effects on the ability to drive and operate machines:
Conclusive studies of the effect of S. John's wort on the ability to drive or use machines are not available.

Adverse effects:
In rare cases Allergic skin reactions, gastrointestinal complaints, fatigue or restlessness may occur.

Particularly fair skinned individuals with increased skin sensitivity may react with dysesthesia (e.g. tingling, sensitivity to cold or pain, burning sensation) and redness (photosensitization) under intense UV exposure (sunbathing, sunlamp, tanning salons).

The color of the urine may become more intensively yellow under certain circumstances. This is due to the natural dye riboflavin (vitamin B12) contained in the tablet coating and is therewith harmless.

In the package information leaflet patients are advised to inform a doctor, when they notice any of the listed adverse effects, so that the doctor can decide on the degree of severity and if further actions are needed.

Overdose:
There are no known reports of acute St. John's wort preparations poisoning in humans. The patient information leaflet advises that following a substantial overdose, the skin should be protected from UV- and sunlight for a duration of 1 to 2 weeks (limit outside activities, sun protection with clothing and use of high-SPF sunscreen, so-called sun-blocks). The described adverse effects may occur with increased strength and incidence. The patient information leaflet advises that a physician should be informed pre-emptively.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties: Pharmacotherapeutic Group: Herbal Antidepressants, ATC-Code: N06AP01

Clinical trials and practical application experience of physicians support an anti-depressive action of water-ethanol extracts of St. John's wort. The underlying action mechanism is not well understood so far. Whole extracts effect monoamine-oxidase as well as COMT inhibition; MAO-inhibition effects of selective hypericin has proven to be substantially less than that of whole extract. The COMT inhibition is attributed to flavonoids.
MAO- and COMT-inhibition measured in-vitro are, however, not sufficient to explain the anti-depressive effect of St. John's wort preparations with this model alone, as it is assumed that pharmacologically relevant inhibitory concentrations are not reached in-vivo.

Additional action mechanisms are being considered based on experimental studies, primarily the inhibition of synaptosomal serotonin-, noradrenaline-, dopamine- and GABA reuptake, adaptive modifications at the receptor level, neurohormonal and neuroimmunological action.
In animals, St. John's wort preparations antagonized reserpine-induced hypothermia, affected anaesthesia duration and shortened the Porsolt-test immobilization phase.

Pharmacokinetic properties:
Hypericin and pseudohypericin: After oral administration of LAIF® 600 (1 x 1 film-coated tablet), the maximum plasma level of hypericin (3.1 ± 1.6 ng/ml) was found after 8.1 ± 1.8 hours. The maximum concentration (8.5 ± 4.4 ng/ml) of pseudo-hypericin was reached after 3 ± 1.4 hours. The half-life is 23.8 ± 5.5 hours for hypericin and 25.9 ± 10.2 hours for pseudohypericin.

Due to their lipophilic nature, hypericins cross the blood brain barrier and can thus reach their sites of action in the central nervous system (CNS).

Hyperforin: After oral administration of LAIF® 600 (1 x 1 film-coated tablet), the maximum plasma level (83.5 ±27.8 ng/ml) was reached after 4.4 ± 1.5 hours. The measured half-life was 19.6 ± 6.4 hours.

A constant plasma level (steady state) (hypericin: approx. 2.8 ng/ml, pseudohypericin: approx. 1.5 ng/ml and hyperforin: approx. 14.8 ng/ml) was attained through daily administration of LAIF® 600 (1 film-coated tablet per day) over a period of 14 days.

As this study and other relevant long-term studies show, these constituents do not cumulate in the body.

Preclinical safety data:
Acute toxicity studies of the St. John's Wort extract used in LAIF® 600 demonstrated that doses up to 2 g/kg body weight were practically nontoxic. Moreover, studies on chronic toxicity up to one year as well as pharmacological safety studies gave no evidence of any toxic effect or potential of the extract to impair specific organ function at subacute doses.

A study has been conducted with 20 male subjects, where 612 mg St. John's wort extract STW 3 (LAIF® 600), corresponding to approx. 1.5 mg hypericin/pseudohypericin, were administered daily for 14 days. At the time of treatment termination, the median UV-dose triggering an erythema (MED) was not significantly changed compared to the baseline value.

Administration of 1,800 mg of another defined methanolic St. John's wort (Not LAIF® 600) extract to healthy subjects of both genders, corresponding to approx. 5.4 mg hypericin/pseusohypericin, over a period of 15 days has shown significantly increased UV-sensitivity at the end, causing an increase in pigmentation. The recommended daily dose of 1 film-coated tablet LAIF® 600 constitutes intake of a maximum of 2.4 mg total hypericin, calculated as hypericin.

The extract did not exert any harmful influence on the fertility and reproduction, gravidity, the fetus and progeny in animal studies, nor have any such harmful effects been reported in the literature. No evidence was found for a mutagenic or genotoxic potential.

PHARMACEUTICAL PARTICULARS
List of excipients: Croscarmellose sodium, Eudragit® E 100, Colloidal anhydrous silica, Lactose monohydrate, Macrogol 4000, Magnesium Stearate, Maltodextrin, Riboflavin, Talc, Titanium dioxide.
Each film-coated tablet contains Lactose Monohydrate 64 mg.

Incompatibilities: None known.

Special precautions for storage: Do not store LAIF® 600 above 25°C! Protect against moisture!

Nature and contents of the container: PVC/PVDC-aluminum Blister packs.

Special precautions for disposal: None.

Israeli Drug Registration Number: 148.58.33063.00

Manufacturer: Steigerwald Arzneimittelwerk GmbH, Germany (including Klocke Pharma-Service GmbH and Klocke Verpackungs-Service GmbH, Germany).

Israeli Marketing Authorization Holder:
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Last revised: 04/01/2015
LAIF600-SPC-01/15