1. Remotiv® 250
Remotiv® 500

Film coated tablets
Herbal medicinal product

2. Composition

Composition

Active substance of Remotiv 250 mg: St. John's wort (Hypericum perforatum), dry extract. One film-coated tablet contains 250mg of the standardized dry extract (Ze 117), standardized to 0.5mg total hypericin. The unique patented extraction process (extraction solvent: ethanol 50% w/w; drug-extract ratio: 4-7:1) guarantees a consistently high-quality product, which has a very low hyperforin content (see below “Drug interactions”).

Active substance of Remotiv 500mg: St. John's wort (Hypericum perforatum), dry extract. One film-coated tablet contains 500mg of the standardized dry extract (Ze 117), standardized to 1mg total hypericin. The unique patented extraction process (extraction solvent: ethanol 50% w/w; drug-extract ratio: 4-7:1) guarantees a consistently high-quality product, which has a very low hyperforin content (see below “Drug interactions”).

For list of excipients: see section 6.1

This medicine contains approx. 120 mg digestible carbohydrates per single dose. The medicine is suitable for diabetics.

3. Pharmaceutical form

Galenic form and active substance per unit

Film coated tablets.
Herbal medicinal product

Remotiv 250:

1 film coated tablet contains 250 mg of the quantified dry extract from St. John’s wort (corresponding to 0.25 - 0.75 mg total hypericins (calculated as hypericin) and maximum 0.5 mg hyperforin.

Remotiv 500:

1 film coated tablet contains 500 mg of the quantified dry extract from St. John’s wort (corresponding to 0.5 - 1.5 mg total hypericins (calculated as hypericin) and maximum 1 mg hyperforin.

4. Clinical particulars

4.1. Therapeutic Indications

For the treatment of symptoms of mild to moderate depression including dejected mood, mood lability, anxiety, inner restlessness, states of tension, and difficulty in falling asleep and sleeping through the night which is associated with these conditions. Treatment is recommended for up to 24 weeks.

4.2 Posology and Method of administration

- One tablet of Remotiv 250 mg morning and evening.
- One tablet of Remotiv 500 mg morning or evening. The tablets should be swallowed, without chewing, with a little liquid, preferably during or after a meal. Remotiv 500 mg tablet is not easily split.
- The product should be taken for at least 14 days, since onset of action may be deferred until then. A minimum length of therapy of 4-6 weeks is recommended. The treatment period is recommended for up to 24 weeks.
- Remotiv may be prescribed for longer periods following the physician's assessment of the benefit-safety profile in long tern use.

4.3 Contraindications

Remotiv 250 / Remotiv 500 must not be taken in cases of:

- known sensitivity to St. John's wort extracts or to one of the ingredients (excipients) of the medicinal product
- known light hypersensitivity
- children under 6 years of age, since there is no data available for this patient group.

Remotiv 250 / Remotiv 500 must not be taken concomitantly with the following medicinal products:

- antidepressants and other serotonergic agents

For details see under «Interactions».

4.4 Special warnings and precautions

As is the case during medication with all drugs for the treatment of depressive episodes, increased suicidal ideations or suicide attempts can occur.

Precautions

Remotiv 250/ Remotiv 500 must be discontinued at least 5 days before any surgery and started again only after consultation of a physician.

Very rarely and especially in fair-skinned persons, unwanted reactions of the skin (sunburn-like redness) or eyes may occur after ingestion of St. John's wort preparations and subsequent exposure to sun light. If such symptoms occur, the treatment must be discontinued. During treatment with Remotiv 250/ Remotiv 500, the skin and eyes should therefore be protected from extensive sun exposure.

St. John's wort preparations should only be taken with caution together with serotonin-uptake inhibitors or other serotonergic drugs as in very rare cases, undesired effects (serotonin syndrome) can occur. For details see «Interactions».

Remotiv 250 contains lactose: patients with the rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Remotiv 500 contains croscarmellose sodium: this medicine contains less than 1 mmol sodium (23 mg) per film coated tablet, i.e. it is almost «sodium-free».

Liver and kidney impairment

Although St. John's wort extracts have been used for years, there are no clinical trials in patients with impaired liver or kidney function. Therefore, in these patients Remotiv should only be taken with care and only under medical supervision.

Elderly patients:
There is usually no need to adjust the dosage in elderly patients.

Children:
This product is not intended for use in children (<12 years).

4.5 Interactions with other medicinal products

Pharmacokinetic interactions
Data available on interactions of St. John's wort extracts with a high hyperforin content indicate an induction of the cytochrome P 450 system by St. John's wort extracts (especially CYP3A4) on one hand, and on the other an induction of transport proteins (P-glycoprotein, e.g. with digoxin). This can lead to a reduction in plasma concentrations, and to a weakening of the therapeutic effect of several co-medicated drugs, as well as potentially severe consequences – especially for substances with a narrow therapeutic range. For the St. John's wort extract Ze 117 contained in Remotiv 250/ Remotiv 500 which is low in hyperforin, it could be shown in 3 clinical interaction studies that the pharmacokinetics of 10 drugs which are metabolized by the cytochrome P 450 system or which are transported by P-glycoprotein are not altered in a clinically

relevant manner (see «Contraindications» and «Characteristics/ effects». Potential interactions with substances which are not metabolized or transported by means of the pathways investigated in the 3 interaction studies can not be excluded.

Pharmacodynamic interactions:

- antidepressants and other serotonergic substances (such as buspirone, amitriptiline, nortripitiline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, triptans, nefazodone, duloxetine, venlafaxine, L-tryptophan, lithium, tramadol, linezolid and others)

St. John's wort preparations should only be taken with caution and under regular supervision together with serotonin-uptake inhibitors or other serotonergic drugs. Very rarely undesired effects (serotonin syndrome) with autonomic dysfunctions (such as perspiration, tachycardia, diarrhoea, fever), mental (such as agitation, disorientation), and motor alterations (such as tremor, myoclonias) can occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.

4.6 Pregnancy/ lactation

Pregnancy

There is no clinical data available on the treatment during pregnancy. The few available animal experiments did not show any direct or indirect toxicity with effect on pregnancy, embryonic and foetal development and/ or postnatal development. The potential risk for humans is not known. Caution is indicated during pregnancy.

Lactation

It is also unknown if ingredients of Remotiv® 250/ 500 pass into mother's milk. For the treatment during pregnancy and lactation a physician must be consulted.

4.7 Effect on the ability to drive and operate machines

In a study with 19 healthy volunteers no influence of Remotiv® 250 and Remotiv® 500 on the fitness to drive and to operate machines was observed.

The ability to react, the fitness to drive and operate machines could, however, be impaired in general due to the primary disease for which the treatment is intended, as well as in connection with the described side-effects.

4.8 Undesirable effects

Evaluation of adverse events is based on the following incidence reports: "Very common" (≥1/10), "common" (<1/10, ≥1/100), "uncommon" (<1/100, ≥1/1000), "rare" (<1/1000, ≥1/10‘000), "very rare" (<1/10‘000).

Nervous system disorders:
Common: headache

Uncommon: dizziness

Psychiatric disorders:
Uncommon: restlessness

General disorders:
Common: asthenia

Uncommon: fatigue

Gastrointestinal disorders:
Common: gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Common: hyperhidrosis

Uncommon: allergic skin reactions

Rare: photosensitivity reaction

In cases of undesirable reactions of the skin, the film coated tablets are to be discontinued and the symptoms should be examined by a physician.

Eye disorders:
In literature, undesired reactions of the eyes were linked to the intake of St. John's wort preparations and concomitant sunlight exposure. In cases of undesirable reactions of the eyes, the film coated tablets are to be discontinued and the symptoms examined by a physician.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

4.9 Overdose

So far only one case of toxic overdose is known to have been accompanied with seizures and confusion. It is assumed that the above-described side-effects would be intensified in cases of considerable overdose. Additionally, an increased light sensitivity must be considered. In this case skin and eye exposure to sun or other UV irradiation (as found in solariums) should be avoided for about 1-2 weeks.

5. Pharmacological properties

ATC-Code
N06AX25

St. John's wort, herbal medicinal product for the treatment of mood disorders.

5.1 Pharmacodynamics

The mechanism of action is still unclear. According to experimental findings in animals, the re-uptake inhibition of the monoaminergic neurotransmitters noradrenalin, serotonin and dopamine into the pre-synaptic neurons is discussed. Also, there is *in-vitro* data on a down-regulation of central beta-adrenoreceptors. The clinical effect is attributed to the increase of neurotransmitter concentration in the synaptic cleft and to the modulating effect of the neurotransmitters at the postsynaptic membrane.

Clinical efficacy

The study data described below do not refer to the licensed field of application mood swings for Remotiv 250/ Remotiv 500, but were obtained with the treatment of minor and moderate depressive episodes, and are intended as background information for appropriate dispensing and administration.

In a double-blind, randomized, placebo-controlled, multi-centre study with two-arms, efficacy and safety of the active substance Ze 117 (2 x 250 mg/ day) were investigated in 162 patients for the treatment of minor and moderate depressive episodes (ICD-10/F32.0 and F32.1) compared to placebo. The HAMD-21 score (Hamilton Score of Depression) had to be between 16 and 24 points at the beginning of the study. The score was reduced in the active substance group (Ze 117; n = 81 patients) from an initial average of 20.13 points (95% confidence interval (CI): 19.50 - 20.76 points) to 10.53 points (95% CI: 9.28 - 11.78 points), and in the placebo group (n = 81 patients) from an initial point value of 18.76 (95% CI: 17.88 - 19.45 points) to 17.89 points (95% CI: 16.51 - 19.28 points) ($p < 0.0001$). The responder rates were 56% in the active substance group and 15% in the placebo group.

Thus, Ze 117 shows a statistically significant and clinically relevant superiority compared to placebo with respect to both decrease in HAMD score and responder rate. With respect to safety, the Ze 117 group

demonstrated a side-effect rate which was comparable to the placebo group (Ze 117: n = 6 (7.4%) and placebo: n = 5 (6.2%)).

In a double-blind, randomized, controlled, multi-centre study with two arms, efficacy and safety of Ze 117 (2 x 250 mg/ day) were compared to the SSRI fluoxetine (20 mg/ day) over a period of 6 weeks in 240 patients with minor and moderate depressive episodes (ICD-10/F32.0 and F32.1). The HAMD-21 score had to be between 16 and 24 points at the beginning of the study, and was reduced from almost identical initial score values of 19.6 to 11.5 in the Ze 117 group (n = 126 patients), and from 19.5 to 12.2 in the fluoxetine group (n = 114 patients). With these results the Ze 117 extract demonstrated in this study a comparable efficacy compared to fluoxetine (non-inferiority; p = 0.09). However, the responder rates were significantly higher in the Ze 117 group with 60% vs. 40% in the fluoxetine group (p = 0.005). Also, the tolerability profile of Ze 117 was more favourable than that of fluoxetine. Thus, 14% of the patients in the Ze 117 group experienced side-effects (of which a possible association with the study medication was found for 28% of the cases), compared to 25% of patients with side-effects in the fluoxetine group (72% of the cases with a possible association with the study medication) (p < 0.01).

In another double-blind, randomized, multi-centre study with two arms, efficacy and safety of Ze 117 (2 x 250 mg/ day; n = 157) were investigated in 324 patients for the treatment of minor and moderate depressive episodes (ICD-10/F32.0/1 and F33.0/1) compared to the tricyclic antidepressant imipramine (150 mg/ day, n = 167). Starting with almost identical initial values of 22.4 points (Ze 117) and 22.1 points (imipramine), the HAMD-17 score (Hamilton Score of Depression) was reduced to 12.0 points (Ze 117) and to 12.75 points (imipramine), respectively. With these results, a statistically comparable efficacy of Ze 117 versus imipramine (p = 0.20) with also comparable responder rates (43% in the Ze 117 group, and 40% in the imipramine group) was demonstrated.

With respect to safety, 39% of the patients in the Ze 117 group experienced side-effects compared to 63% of the patients in the imipramine group.

Other information

Clinical interaction study with a cocktail of 7 drugs and cytochrome P450 as well as the P-glycoprotein transporter:

In a clinical interaction study using St. John's wort extract Ze 117 which is low in hyperforin and is contained in Remotiv 250/ Remotiv 500 film coated tablets, the influence on 7 drugs was investigated in 20 subjects. The administration of St. John's wort extract Ze 117 together with a cocktail of caffeine 50 mg (CYP1A2), bupropion·HCl 75 mg (CYP2B6), flurbiprofen 10 mg (CYP2C9), omeprazole 10 mg (CYP2C19), dextromethorphan 10 mg (CYP2D6), midazolam 1 mg (CYP3A4) and fexofenadine 25 mg (P-glycoprotein) did not show clinically relevant interactions in the pharmacokinetics of these drugs.

Clinical interaction studies with oral hormonal contraceptives and cytochrome P450:

A non-controlled clinical interaction study with the hyperforin-poor St. John's wort extract Ze 117 (250 mg twice daily) which is contained in Remotiv 250/ Remotiv 500 film coated tablets and an oral hormonal contraceptive (0.02 mg ethinylestradiol and 0.15 mg desogestrel) in 16 healthy female subjects showed no negative influence on the pharmacokinetics of the active ingredients.

The average relative bioavailability rates of Cmax and AUC were elevated by about 10% after 14 days of Ze 117 intake; the confidence intervals of Cmax and AUC remained within the equivalence limits of 20%. The serum concentrations of ethinyl estradiol and 3-ketodesogestrel were equivalent before and after 14 days of concomitant intake of Ze 117 and a hormonal oral contraceptive.

Clinical interaction study with digoxin and the PGP transporter:
In a randomized, double-blind study, the inductive impact of hyperforin-poor St. John's wort extract Ze 117 which is contained in Remotiv 250/ Remotiv 500 film coated tablets on the P-glycoprotein transporter was investigated in 17 healthy subjects. The pharmacokinetic parameters of digoxin were investigated in 7 subjects treated with Ze 117 and in 10 subjects treated with placebo. The subjects were adjusted to a steady-state digoxin trough level of 1.0 ng/ mg ± 20% and subsequently either received digoxin and Ze 117 concomitantly for 14 days, or digoxin and placebo, respectively. However, the respective AUC of digoxin in the placebo and verum groups showed no significant differences ($p = 0.1460$). The percentage change in digoxin trough level after 14 days of concomitant medication compared to Ze 117 baseline was tested for equivalence against the change with placebo. The one-sided t-test resulted in a p-value of 0.05, with which Ze 117 and placebo are equivalent in their influence on the digoxin trough level in the given range of ± 20%. The comparison of Ze 117 with placebo did not show any significant differences between the groups regarding the AUC changes.

5.2 Pharmacokinetics

According to the current scientific knowledge the total extract, in its composition a complex system, is considered to be the active substance. Pharmacokinetic investigations on humans were only conducted for a few putative active ingredients of St. John's wort. At the moment, hypericin and pseudohypericin, amongst others, are regarded as such ingredients.

Absorption
In male volunteers a dose of 250 mg (1 film coated tablet Remotiv 250) and a dose of 500 mg extract (2 film coated tablets Remotiv 250 or 1 film coated tablet Remotiv 500) led to maximum hypericin plasma levels of 0.67 µg/ l and 1.3 µg/ l respectively, with a t_{max} value of 7.1 h and 7.0 h

respectively. With doses of 250 mg (1 film coated tablet Remotiv 250) and 500 mg extract (2 film coated tablets Remotiv 250 or 1 film coated tablet Remotiv 500) hypericin half-life values of 21.4 h and 24.6 h respectively were measured. Additional tests with respect to distribution, metabolism, as well as elimination were not conducted so far, since the therapeutically relevant active substances of the St. John's wort extract have not been clearly identified yet.

Distribution

No studies were performed.

Metabolism

No studies were performed.

Elimination

No studies were performed.

5.3 Preclinical data

Only few preclinical studies have been conducted on the St. John's wort dry extract Ze 117. From these studies with respect to mutagenicity, embryotoxicity, and teratogenicity, no risks for humans could be derived.

6. Pharmaceutical particulars

6.1 List of exipientsRemotiv 250mg: microcrystalline cellulose, lactose monohydrate, macrogol 6000, hypromellose, titanium dioxide, magnesium stearate, silica colloidal anhydrous, macrogol 400, propylene glycol, macrogol 20000, iron oxide red.

Remotiv 500mg: microcrystalline cellulose, croscarmellose sodium, macrogol 6000, magnesium stearate, silica colloidal anhydrous, stearic acid, hypromellose, titanium dioxide, macrogol 20000, iron oxide red.

6.2 Shelf-life

The medication should only be used up to the date indicated as «EXP» on the package.

6.3 Special storage information

Store below 25 °C in the original package.

Keep out of reach and sight of children.

6.4 Packages

Remotiv 250:

Blister packages containing round biconvex pink 60 film coated tablets,

Remotiv 500:

Blister packages containing oblong biconvex pink 30 film coated tablets

Registration no.: 250 mg **130-71-30720**

Registration no.: 500 mg **141-28-31607**

7. Manufacturer : Max Zeller Söhne AG, CH-8590 Romanshorn

Registration Holder: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301

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