Product Information

Remotiv 250
Remotiv 500
Film-coated tablets

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").

Inactive ingredients Remotiv 250mg: microcrystalline cellulose, lactose monohydrate, hypromellose, macrogol 6000, titanium dioxide, magnesium stearate, macrogol 400, propylene glycol, macrogol 20000, iron oxide red.

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

Pharmacodynamic actions

ATC-Code: N05CM
Herbal sedative

St John's wort may modulate brain levels of neurotransmitters but the precise mechanism of action of St John's wort is not known. The extract Ze 117 contains many ingredients which may be responsible for the pharmacological action of Remotiv. Animal studies suggest that the therapeutic effect of Remotiv is based on the inhibition of the reuptake of norepinephrine and serotonin into the presynaptic neurons, as well as a down-regulation of central beta-adrenergic receptors. Medical literature has described other possible mechanisms of action for St. John's wort.

Pharmacokinetic properties

St. John's wort contains a number of phytochemical components, but hypericin is considered to be one of the main biological constituents. Hypericin can be used as a marker in order to determine the pharmacokinetics of the extract.
In male volunteers administered a Remotiv dose of 250mg and 500mg, peak plasma levels of hypericin were 0.67 mcg/l and 1.3mcg/l, respectively, at t_{max} values of 7.1 hours

and 7.0 hours, respectively. The measured half-life values of hypericin were 21.4 hours and 24.6 hours, respectively. Following multiple bid dosing with 250 mg, mean hypericin plasma concentrations were 2.6 mcg/l. Steady state was achieved within 14 days without undue accumulation.

Clinical Trials
Remotiv has been shown to be as effective as fluoxetine and imipramine for the treatment of mild to moderate depression in short-term controlled clinical trials. Remotiv was associated with fewer adverse events in these trials. An open, 12-month study in 141 patients established the long-term safety of Remotiv. Remotiv maintained symptom improvement relative to baseline over this period. However, because there was no comparator arm, this study did not establish the long-term efficacy of the product.

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.

Contraindications
Known hypersensitivity to products based on St. John's wort or to one of the excipients contained in Remotiv.

Known photohypersensitivity.

Remotiv must not be taken concomitantly with the following medicinal products:
- certain immunosuppressants (e.g. cyclosporine, tacrolimus or sirolimus)
- anti-retroviral HIV-drugs from the group of non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and proteinase inhibitors (e.g. indinavir)
- certain cytostatics (e.g. imatinib, irinotecan)
- oral anti-coagulants of the coumarin type
(see Drug Interactions).

Children under 6 years of age, since there is no data available for this patient group.

Special warnings and precautions for use
Although extracts of St. John's wort have been used for many years without evidence of an adverse effect on the liver or kidney, there are no controlled clinical studies available in patients with impaired hepatic or renal function. Therefore, in such patients Remotiv should be used with caution and under medical supervision.
In patients concurrently taking other drugs, especially drugs with a narrow therapeutic window, extracts of St. John’s wort should be taken only after careful consideration due to the possibility of potential drug interactions (see Drug Interactions). Plasma levels and/or the effect of the interactive drug should be monitored closely at the beginning of Remotiv therapy, when any change in dosage occurs and after Remotiv therapy is discontinued.
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, the skin and eyes should therefore be protected from extensive sun exposure.

It has been demonstrated that Remotiv does not affect driving ability or ability to use machinery safely. However, in isolated patients the underlying mood disorder or the medicine's side effects may adversely affect the patient's ability to drive or use machinery and these patients should be cautioned.

Pregnancy and Lactation
Reproduction studies in animals have indicated no risks to the fetus. However, scientific evidence documenting the safe use of Remotiv during pregnancy and lactation in humans is not available. Therefore, the use of Remotiv in pregnant and nursing women should be avoided.

Use in Pediatrics
This product is not intended for use in children (<12 years).

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

Drug Interactions
Current data indicates that St. John's wort preparations may induce hepatic cytochrome P450 enzymes, specifically CYP3A4, and transport proteins, specifically P-glycoprotein. This can result in drug interactions. Specifically, starting therapy with a St. John's wort preparation can lead to a reduction in plasma levels of a concomitant medicine, and, conversely, stopping therapy with a St. John's wort preparation can lead to an increase in plasma levels of a concomitant medicine.
In case of an accidental intake of St. John's wort preparations together with interactively acting substances, the St. John's wort preparation should, generally, be discontinued gradually.
Hyperforin (one of the constituents in St John's wort) has been demonstrated to be responsible for many of the observed drug interactions. Therefore, due to its low hyperforin content, Remotiv may have less potential for drug interactions than other St. John's wort preparations.

Immunosuppressants (Cyclosporin and Tacrolimus and Sirolimus)

Patients with a suppressed immune system from cyclosporine, tacrolimus or sirolimus must not be treated with St. John's wort at the same time. St. John's wort leads to a rapid and marked decrease in plasma levels and loss of the immunosuppressive effect with potentially severe consequences (transplant rejection).

Anti-retroviral HIV-drugs from the group of non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and proteinase inhibitors (e.g. indinavir)

When treated with non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and proteinase inhibitors (e.g. indinavir), the intake of St. John's wort preparations is contra-indicated since St. John's wort can lead to a decrease in plasma levels.

Cytostatics (Irinotecan/Imatinib)

During treatment with irinotecan and imatinib, Remotiv is contraindicated. Interactions with other chemotherapy agents metabolized by CYP enzymes or P-glycoprotein are possible and should be avoided.

Anticoagulants of the coumarin type (e.g. warfarin acenocoumarol, phenprocoumon)

Patients taking oral anticoagulants must not be treated with St. John's wort, since it influences their coagulation inhibiting effect (and increases the risk of thromboembolism).

Antidepressives and other serotonergic substances (such as buspirone, amitriptyline, nortriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and others)
Simultaneous use of St John's wort and other anti-depressants such as selective serotonin re-uptake inhibitors (SSRIs) may lead to excessive serotonin stimulation and possible toxicity (serotonin syndrome) with autonomic dysfunction (such as perspiration, tachycardia, diarrhoea, fever), mental alterations (such as agitation, disorientation), and motor alterations (such as tremor, myoclonias). Concomitant use is not generally recommended and a sufficient washout period in-between Remotiv and other anti-depressants should be allowed in order to avoid serotonin syndrome. Similar precautions should be exercised for other serotonergic drugs such as buspirone. Selective serotonin 5-HT1 agonists used to treat migraine may theoretically also cause serotonin syndrome in concomitant use.
Should the prescriber nevertheless decide to concomitantly prescribe Remotiv with an SSRI/SNRI or other serotonergic drug after a careful individual risk/benefit assessment, caution should be exercised and the patient should be closely monitored.

Methadone
Other preparations of St. John's wort (not Remotiv) have been documented to cause a significant reduction in the plasma levels of methadone.

Digoxin
Prescribers should be aware that St. John's wort preparations may interact with digoxin. Apparently due to Remotiv's low hyperforin content, there is no evidence for a pharmacokinetic interaction between Remotiv and digoxin. A pharmacokinetic study showed that Remotiv (250 mg bid) had no effect on serum levels of digoxin. Drug interaction studies cannot predict with 100% certainty the response of an individual patient.

Hormonal Contraceptives
St. John's wort can lead to reduced efficacy of hormonal contraceptives (e.g. oral products, injected depot preparations, sub cutaneous implants, transdermal, intrauterine, and vaginally applied products with hormone release). Several cases of interim bleeding with so-called low-dose micro pills (ethinylestradiol content 30 µg or lower) were reported internationally. Even individual cases of undesired pregnancies with hormonal contraceptives and concomitant intake of St. John's wort were reported.

Apparently due to Remotiv's low hyperforin content, there is no evidence for a pharmacokinetic interaction between Remotiv and oral contraceptives. A pharmacokinetic study with a combined low-dose oral contraceptive

(Lovelle=Mercilon=Feminet) showed that Remotiv (250 mg bid) did not affect the serum levels of the estrogenic or progesterone components of the oral contraceptive, and did not lead to spotting. Drug interaction studies cannot predict with 100% certainty the response of an individual patient.

Benzodiazepines
Other preparations of St. John's wort (not Remotiv) have been documented to cause a significant reduction in the plasma levels of benzodiazepines that are metabolized via CYP3A4 such as alprazolam and midazolam. St. John's wort should only be given with caution together with benzodiazepines

Anticonvulsants
There is also a theoretical possibility of an interaction between St. John's wort and antiepileptics such as carbamazepine, phenobarbital and phenytoin. Stopping St. John's wort abruptly may result in increased and possibly toxic, concentrations of the interacting drug.

Steroid hormones
It cannot be excluded that St. John's wort preparations also influence the metabolisms of orally or intravenously applied steroid hormones. St. John's wort should only be given with caution together with steroid hormones.

Statins
Other preparations of St. John's wort (not Remotiv) have been documented to cause a significant reduction in the plasma levels or effects of simvastatin and atorvastatin, but not pravastatin.

Agents used for photodiagnostic procedures or for phototherapy
There is a possibility that concurrent use of Remotiv with agents used for photodiagnostic procedures or for phototherapy, eg porfimer, could lead to an increased risk of photosensitivity.

General
Surgeons/anesthesiologists should discuss with patients scheduled for surgery the need to initiate changes in dosing and administration of Remotiv during the peri-operative period. Remotiv must be discontinued at least 5 days before any surgery and started again only after consultation of a physician

The amount of active ingredient may vary widely between different preparations containing St John's wort. Switching from Remotiv to an alternative St. John's wort preparation may therefore alter the degree of enzyme induction of other drugs taken concurrently.

Adverse effects
The most common adverse effects are gastrointestinal disturbances (4-6%), followed by headache, sweating, and asthenia (1-2%). Dizziness (<1%) and restlessness may also occasionally occur.

If redness of the skin appears, therapy should be discontinued and the cutaneous symptoms should be followed-up.
As for other anti-depressants, isolated cases of mania associated with the use of St. John's wort have been reported.

Dosage and 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-term use.

Overdose

No acute or chronic toxic manifestations have been reported in humans but those side effects listed above could manifest with greater intensity. In addition, photosensitivity is also possible. In this case skin and eye exposure to sun or other UV irradiation (e.g. as found in solariums or tanning salons) should be avoided for about 1-2 weeks.

Presentation

Remotiv 250: Film coated tablets: 20, 60
Remotiv 500: Film coated tablets: 10, 30

Store below 25°C in the original package.

Manufacturer

Max Zeller Sohne AG, Romanshorn, Switzerland

Registration Holder

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Registration numbers:

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