Karmamood film-coated tablets

Lloydspharmacy St John’s wort film-coated tablets

THR 23056/0011

UKPAR

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KARMAMOOD FILM-COATED TABLETS

LLOYDSPHARMACY ST JOHN’S WORT FILM-COATED TABLETS

THR 23056/0011

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Schwabe Pharma (UK) Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal products Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets (Traditional Herbal Registration number: 23056/0011). These products, which are identical to each other, are available without prescription and can be bought from pharmacies and other outlets.

Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets are used to relieve the symptoms of slightly low mood and mild anxiety, based on traditional use only. The tablets’ active ingredient is dry ethanolic extract of the plant St John’s wort, also known as *Hypericum perforatum* L. This registration is based exclusively upon evidence of traditional use of St John’s wort as a herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration scheme to prove scientifically that the product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.
KARMAMOOD FILM-COATED TABLETS

LLOYDSPHARMACY ST JOHN’S WORT FILM-COATED TABLETS

THR 23056/0011

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal products Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets to Schwabe Pharma (UK) Ltd on 27 July 2009. These products are on the general sales list (GSL). The application was submitted under Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme.

These products consist of tablets containing 250 mg of dry extract from St John’s wort (Hypericum perforatum L.) The products are used for relief from the symptoms of slightly low mood and mild anxiety.

This THR is based exclusively on evidence of traditional use of St John’s wort. The recommended dose is one tablet daily.

The data supplied by the applicant demonstrate 30 years of traditional use of St John’s wort in the European Community. A satisfactory review of the available safety data on St John’s wort has also been provided, together with an expert safety report supporting the proposed products.
PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE

General information
Scientific name of the plant: Hypericum perforatum L.
Family: Hypericaceae (syn. Guttiferae).
Synonyms of the herbal substance: St. John’s wort
Parts of the plant used: Dried entire or comminuted aerial parts, collected shortly before or during the blossoming period

Manufacture
The herbal substance comes from the aerial parts of the plant St John’s wort (Hypericum perforatum L.), which belongs to the Hypericaceae (syn. Guttiferae) family. The plant grows in middle Europe, Western Asia and North America on sunny dry or barren meadows.

The plant material used for extraction in this product is obtained from Europe or North America between spring and summer and from South America or Africa from November to January. It is obtained mainly from cultivated material but it is also collected from the wild. The aerial parts are collected during the flowering period. After harvesting, the herb is dried quickly under mild conditions.

During cultivation the crops are treated with fertiliser, herbicide and fungicide but insecticides are not used. Assurance has also been provided that the herbal drug has not been treated with ethylene oxide or irradiation. Furthermore, the plant is collected only during the flowering period, which is compliant with the Ph Eur.

The information provided on the collection of the plant starting material is considered to be acceptable and assurance has been given that cultivation and harvesting are performed according to Good Agricultural and Collection Practice (GACP).

Control of Herbal Substance
The starting material complies with the European Pharmacopoeia monograph.

Satisfactory certificates of analysis for the herbal substance have been provided.

Container Closure System
Details are provided on the container closure system used for storage of the herbal drug along with confirmation that all components comply with Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
No shelf life has been given for the dried herbal substance as it is a precursor of the active substance, the herbal preparation.
HERBAL PREPARATION

General information
Herbal preparation: St John’s Wort dry extract
Scientific name of the plant: *Hypericum perforatum* L.
Parts of the plant used: Dried entire or comminuted aerial parts, collected during the blossoming period
Ratio of the herbal substance to herbal preparation (native): 3.5-6:1
Extraction solvent: Ethanol 60 % v/v

Manufacture
Manufacture of the extract is a standard procedure. A satisfactory description of the manufacturing process of the herbal substance and flow diagram has been provided.

Certificates of analysis for all materials used in the manufacture of the herbal preparation are provided. All excipients are tested and released according to their Ph. Eur. monograph.

Satisfactory in-process controls are in place during manufacture to ensure the quality of the herbal preparation.

Control of Herbal Preparation
A satisfactory specification with appropriate tests and limits has been provided for the herbal preparation.

Satisfactory analytical procedures are used to control the quality of the herbal preparation. Analytical procedures have been validated, as appropriate.

Certificates of analysis have been provided for production batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specification.

The proposed specification has been justified satisfactorily.

Container Closure System
Specifications have been provided by the supplier of the container closure system together with the declaration of compliance with Directive 90/128 EC, as amended.

Assurances have also been provided from the suppliers that the packs and their contents/labels etc are suitable for food use.

Stability
Batches were packed in the container closure system and stored in ICH conditions. The data support the proposed retest period of 12 months when stored below 25°C protected from heat, light and moisture.
HERBAL PRODUCT

Description and Composition of the Herbal Product
The tablets comprise lactose monohydrate, calcium hydrogen phosphate dehydrate, powdered cellulose, colloidal anhydrous silica, magnesium stearate, sodium starch glycolate (type A), stearic acid, Eudragit E 100, hypromellose, macrogol 6000, talc, titanium dioxide E 171 and iron oxide hydrate E 172.

The choice of excipients is based on experience and compatibility of the chosen excipients with the drug substance is confirmed by stability testing. Interaction of the herbal product with the container is not expected based on the results of stability testing.

Control of Excipients
All the excipients and analytical procedures are as specified by their respective Ph Eur monographs. The colouring agents, titanium dioxide E 171 and iron oxide hydrate E 172, comply with Directive 95/45/EC. Certificates of analysis of the excipients have been provided by the suppliers.

The applicant has confirmed that the magnesium stearate used to make the herbal products is of vegetable origin. Appropriate certification has been provided from the supplier confirming this.

Manufacture
The manufacturing method is a standard procedure for direct tabletting, coating and blistering.

A number of in-process control tests are performed during the manufacturing process to ensure the quality of the products. All are considered adequate.

Control of Herbal Product
The finished product specifications at release and end of shelf life are detailed and the tests and limits used were found to be satisfactory for a product of this nature.

Satisfactory details have been provided on all analytical procedures and these analytical procedures are valid.

Certificates of Analysis have been presented for batches of the drug product demonstrating little inter-batch variation.

Reference Standards or Materials
Certificates of Analysis for all the markers, including the reference substance, have been provided by the finished product manufacturer.

Container Closure System
The products are presented in packs of 28, 30, 56, 60, 90 or 120 tablets sealed into binary blisters made of PVC/PVDC and aluminium. Suitable specifications have been provided by the packaging suppliers. The components of the primary packaging...
system, including the sealing layer, comply with Directive 2002/72 relating to contact with foodstuffs.

**Stability**
Stability studies were conducted under ICH conditions on product batches in the container type proposed for marketing.

Based on the results, a proposed shelf life of 3 years with the storage condition “Do not store above 25°C” is justified.

**PRODUCT LITERATURE**
The product literature (Summary of Product Characteristics, Patient Information Leaflets and labelling) for these products are pharmaceutically satisfactory.

Package leaflets have been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contains.

**ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY**
These products are satisfactory and a Traditional Herbal Registration can be granted.
NON-CLINICAL ASSESSMENT

NONCLINICAL ASPECTS
The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of St John’s wort.

NONCLINICAL OVERVIEW
The applicant has submitted a good literature review with this application. An Expert Report on Safety was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a medical doctor with expertise in herbal medicines and is dated 14 July 2003.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on St John’s Wort, it is not possible to assess if the safety package for the phytochemical constituents of St John’s wort is acceptable to the standards of today’s GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in compliance with guideline EMEA/HMPC/32116/05.

Data in the literature for genotoxic and carcinogenic potential of the product is deficient as basic genotoxicity tests have not been conducted. The company have provided their assurance that they will address this lack of data before renewal of their licence.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPCs for these products are satisfactory from a preclinical point of view.

ENVIRONMENTAL RISK ASSESSMENT
An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

CONCLUSION
The information supplied demonstrating traditional use of St John’s wort is acceptable. An adequate literature review of St John’s wort has been carried out by the applicant and no new non-clinical data was submitted for assessment with this application. Granting of a THR is acceptable.
CLINICAL ASSESSMENT

PROPOSED INDICATION
The applicant has proposed the following:

“A traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety, based on traditional use only.”

This indication is appropriate.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant has proposed the following:

“For oral short term use only.

For adults and the elderly, take 1 tablet daily. The tablets should be swallowed whole with a little liquid. The tablets should not be chewed.

The patient should consult a doctor if symptoms worsen or do not improve after 6 weeks.

Not for children or adolescents under 18 years.”

This is appropriate.

EFFICACY
No clinical efficacy data is required for registration of traditional herbal medicinal products.

EVIDENCE OF TRADITIONAL USE
St John’s wort (Hypericum perforatum L.) is generally accepted to have a tradition of use as a herbal medicine.

Article 16 c 1 (c) requires the applicant to provide bibliographic or expert evidence to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community.

The applicant has provided a bibliographic review of the evidence for the use of St John’s wort within the EU for a period exceeding 30 years. The principal points of this review are as follows:

- In the UK, four current Product Licenses of Right are currently licensed and have been on the market for more than 30 years.
- In Germany, in 2005, 126 medicinal products for oral use containing St John’s Wort as the active ingredient appeared on the German agency’s database. At least 48 of these products were registered in Germany in 1978.
• In Germany, Hyperforat, Neurapas and Psychotonin, which all contain St John’s Wort, have been identified as being on the German market for more than 30 years.
• Hyperforat Liquid and Neurapas demonstrate that the daily dosage proposed for Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets has been used medicinally for at least 30 years in an EU country.
• The indication for the products on the market in Germany is similar to the indication proposed for Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets.
• The 25th Edition of Martindale (1967) refers to an infusion and dosage of St John’s wort which is above the recommended daily dosage of Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets.
• Recognised literature sources indicate that the proposed daily dosage for Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets falls within recommended daily dosages for St John’s wort.
• Older references identify that St John’s wort has a history of traditional use for the proposed indication for Karmamood film-coated tablets and Lloydspharmacy St John’s wort film-coated tablets.

The information provided is sufficient to demonstrate that St John’s wort has been in use for at least 30 years, of which at least 15 years have been in an EU Member State. The applicant has also provided sufficient data to support the use of the 60% ethanolic extract.

SAFETY REVIEW
Article 16 c 1 (D) requires the applicant to provide a bibliography of safety data together with a Safety Expert Report.

A safety review has been provided, as well as an expert report written by a pharmacist with expertise in herbal medicines. A satisfactory expert CV was provided.

The clinical review of safety submitted in the dossier outlined adverse events from controlled and uncontrolled studies relevant to the safety of St John’s wort.

A satisfactory and comprehensive review of the literature has been provided. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. The applicant has, therefore, provided assurance that appropriate genotoxicity testing will be performed prior to renewal of this registration.

PRODUCT LITERATURE
The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for these products is medically satisfactory.

ASSESSMENT OF SUITABILITY FOR GSL STATUS FOR INTERNAL USE
The Herbal Medicines Advisory Committee (HMAC) advised that St John’s wort is suitable for inclusion on the General Sales List (GSL) for internal use.

DISCUSSION
The data supplied by the Applicant are sufficient to demonstrate 30 years of traditional use within the European Community for required for registration under the Traditional Herbal Medicines Product Directive.
OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products (THMP).

The Applicant has provided a bibliographic review which shows ample evidence for the use of St John’s wort within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has been provided.

The SPCs, PILs and labelling are satisfactory.

RISK ASSESSMENT
The quality of these products is acceptable and no new preclinical or clinical safety concerns have been identified.
KARMAMOOD FILM-COATED TABLETS

LLOYDSPHARMACY ST JOHN’S WORT FILM-COATED TABLETS

THR 23056/0011

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Traditional Herbal Registration application on 26 March 2009

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 9 April 2009

3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 23 June 2009. The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 24 July 2009.

4 A THR was granted on 27 July 2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Karmamood film-coated tablets
Lloydspharmacy St John’s wort film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:

250 mg of extract (as dry extract) from St John’s wort aerial parts (*Hypericum perforatum* L.)(3.5-6:1)(equivalent to 875 – 1500 mg of St John’s wort).

Extraction solvent: Ethanol 60% v/v.

Each film-coated tablet contains: Lactose monohydrate (11 mg).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet.
Round, ochre, film-coated tablets, free from ruptures.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
A traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety, based on traditional use only.

4.2 Posology and method of administration
For oral short term use only.

For adults and the elderly, take 1 tablet daily. The tablets should be swallowed whole with a little liquid. The tablets should not be chewed.

The patient should consult a doctor if symptoms worsen or do not improve after 6 weeks.

Not for children or adolescents under 18 years.

4.3 Contraindications
Hypersensitivity to the active ingredient or any of the excipients.

The product should not be used in children or adolescents under 18 years of age.
Pregnancy and lactation (see Section 4.6)

Patients with known dermal photosensitivity or patients undergoing phototherapy or any photodiagnostic procedures.

This product should not be taken concomitantly with the medicines included in Section 4.5. This is because St John’s wort (Hypericum perforatum) has been shown to induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9 and CYP3A4 as well as transport protein P-glycoprotein. This results in pharmacokinetic interactions with a large number of medicines including leading to a possible decrease in the effectiveness of those medicines.

In addition, pharmacodynamic interactions have also been identified with antidepressants, particularly the SSRI antidepressants and with the triptan group of medicines.

4.4 Special warnings and precautions for use

Do not exceed the stated dose.

If the condition worsens, or if symptoms persist for more than six weeks medical advice should be sought.

The dosing and safety of St John’s Wort have not been studied in children/adolescents below 18 years and safety is not established.

This product is intended for relief of symptoms of slightly low mood and mild anxiety. Patients with signs and symptoms of depression should seek medical advice for appropriate treatment.

In very rare cases, particularly in light-skinned persons, sun burn type reactions on skin areas exposed to strong sunlight may occur due to photosensitisation by St John’s wort. Persons using this product should avoid excessive sunbathing or the use of sunbeds or solariums.

This product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia (see Section 4.5).

Each film-coated tablet also contains: Lactose monohydrate (11 mg). Patients with rare glucose-galactose malabsorption and/or with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Substances in St John’s wort (Hypericum perforatum) have been shown to induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9 and CYP3A4 as well as the transport protein P-glycoprotein. This results in pharmacokinetic interactions with a large number of medicines leading to a potential decrease in the effectiveness of those medicines. Clinically significant interactions have
been reported with for example: warfarin, ciclosporin, HIV protease inhibitors, theophylline, digoxin, oral contraceptives, and anticonvulsants.

Users of oral contraceptives taking St John’s wort (*Hypericum perforatum*) may experience intracyclic menstrual bleeding and risk of contraception failure is increased.

Clinically significant pharmacodynamic interactions have also been identified with the SSRI antidepressants, and the triptan group of medicines used to treat migraines. Due to the increased risk of undesirable effects associated with these interactions this product should not be used concomitantly with these types of medicines.

Therefore this product should not be taken concomitantly with the medicines included in Table below.

<table>
<thead>
<tr>
<th>Co-administered drug</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anaesthetics /pre-operative medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl, propofol, sevoflurane, midazolam</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Based on the elimination half-lives of hypericin and hyperforin this product should be discontinued at least 10 days prior to elective surgery.</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td><strong>Anti-anginals</strong></td>
<td></td>
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<tr>
<td>Ivabradine</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
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<tr>
<td><strong>Anti-arrhythmics</strong></td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
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<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
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<tr>
<td>Erythromycin, clarithromycin, telithromycin</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin, acenocoumarol</td>
<td>Reduced anticoagulant effect and need for increased dose</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricycles eg. amitriptyline, clomipramine</td>
<td>Increased serotonergic effects with increased incidence of adverse reactions.</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td>MAOIs eg. moclobemide</td>
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</table>
SSRIs eg. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, Others eg. duloxetine, venlafaxine

### Antiepileptics

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Reduced blood levels with increased risk of frequency and severity of seizures.</th>
<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drugs in this class including:</td>
<td></td>
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<tr>
<td>carbamazepine</td>
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<tr>
<td>phenobarbitone</td>
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<tr>
<td>phenytoin</td>
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<tr>
<td>primidone</td>
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<tr>
<td>sodium valproate</td>
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</tbody>
</table>

### Antifungals

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Reduced blood levels with risk of therapeutic failure.</th>
<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>itraconazole,</td>
<td></td>
<td></td>
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<tr>
<td>voriconazole</td>
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</tr>
</tbody>
</table>

### Antimalarials

<table>
<thead>
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<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>artemether</td>
<td></td>
<td></td>
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<tr>
<td>lumefantrine</td>
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</tbody>
</table>

### Anti-parkinsons

<table>
<thead>
<tr>
<th>Anti-parkinsons</th>
<th>Reduced blood levels with risk of therapeutic failure.</th>
<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>rasagiline</td>
<td></td>
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</tbody>
</table>

### Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Reduced blood levels with risk of therapeutic failure.</th>
<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td></td>
<td></td>
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</tbody>
</table>

### Antivirals

<table>
<thead>
<tr>
<th>Antivirals</th>
<th>Reduced blood levels with possible loss of HIV suppression.</th>
<th>Do not take with this product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV protease inhibitors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir</td>
<td></td>
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</tr>
<tr>
<td>HIV non-nucleoside reverse transcriptase inhibitors: efavirenz,</td>
<td></td>
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</tbody>
</table>

Reduced blood levels with possible loss of HIV suppression. Do not take with this product.
### Anxiolytics
- **buspirone**: Increased serotonergic effects with increased incidence of adverse reactions. Do not take with this product.

### Aprepitant
- **Aprepitant**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

### Barbiturates
- **butobarbital, phenobarbital**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

### Calcium channel blockers
- **amlodipine, nifedipine, verapamil, felodipine**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

### Cardiac glycosides
- **digoxin**: Reduced blood levels and loss of control of heart rhythm or heart failure. Do not take with this product.

### CNS Stimulants
- **methylphenidate**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

### Cytotoxics
- **irinotecan, dasatinib, erlotinib, imatinib, sorafenib, sunitinib, etoposide, mitotane**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

### Hormonal contraceptives
- **Oral contraceptives**
  - Emergency Hormonal Contraception
  - Hormonal implants, injections
  - Transdermal patches, creams etc.
  - Intra-uterine devices with hormones
  Reduced blood levels with risk of unintended pregnancy and breakthrough bleeding. Do not take with this product.

### Hormone Replacement Therapy
- **Hormone Replacement Therapy**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.
<table>
<thead>
<tr>
<th><strong>Oral</strong></th>
<th><strong>Tranadermal patches, gels</strong></th>
<th>Vaginal rings</th>
</tr>
</thead>
</table>

**Hormone antagonists**

- **exemestane**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

**Diuretics**

- **eplerenone**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

**5HT agonists**

- **almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan**: Increased serotonergic effects with increased incidence of adverse reactions. Do not take with this product.

**Immunosuppressants**

- **cyclosporin, tacrolimus**: Reduced blood levels with risk of transplant rejection. Do not take with this product.

**Lipid regulating drugs**

- **simvastatin, atorvastatin**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

**Lithium**

- **Reduced blood levels with risk of therapeutic failure.** Do not take with this product.

**Proton pump inhibitors**

- **lansoprazole, omeprazole**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

**Theophylline**

- **Reduced blood levels and loss of control of asthma or chronic airflow limitation.** Do not take with this product.

**Thyroid hormones**

- **thyroxine**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.

**Oral hypoglycaemic drugs**

- **gliclazide**: Reduced blood levels with risk of therapeutic failure. Do not take with this product.
4.7 Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Undesirable effects associated with the use of St. John’s wort are generally mild. The following undesirable effects have been reported in clinical studies:

Rare (>1/10,000 <1/1,000)
Gastrointestinal disorders:
- Nausea
- Abdominal Pain
- Diarrhoea

Skin and subcutaneous tissue disorders:
- Pruritis
- Rash
- Urticaria

Other ADRs reported in the literature include headaches, neuropathy, anxiety, dizziness, fatigue, mania and allergic reactions.

When St John’s wort is used, sunburn-like reactions in the parts of skin exposed to strong UV irradiation (sun, solarium) can rarely occur, particularly in fair-skinned individuals, due to the increased sensitivity of the skin to sunlight (photosensitization).

4.9 Overdose
There are no data on human overdose with St John’s wort. Where a large overdose has occurred, phototoxic reactions may occur. The skin of the patient should be protected for one week from UV irradiation. Outdoor activities should be restricted and clothes and/or sun block preparations used to protect the skin from sunlight. Symptomatic and supportive measures should be taken as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Herbal medicinal product for the treatment of depressive disorders.
ATC code: N06AP01

The active constituents of St John’s wort have not been definitively established. However, the phloroglucinol constituent, hyperforin, and the hypericin group of constituents, are thought to play an important role in its activity.
5.2 Pharmacokinetic properties
The active ingredients of St John's wort can interact with other medicinal agents in two ways. Firstly, active ingredients in St John’s wort that themselves are metabolised in the liver by the CYP3A4 isoenzyme, increase (induce) the activity of this enzyme so that it accelerates the elimination of other medicinal agents which are degraded by the same pathway. This leads to a consequent reduction in the plasma concentration and effectiveness of these other substances. Secondly, the active ingredients in St John’s wort, like other type SRI or SSRI medicinal agents with an antidepressant action, can raise the concentration of serotonin in certain parts of the central nervous system so that this neurotransmitter can sometimes reach toxic levels, particularly when drugs containing St John’s wort are combined with other antidepressants.

5.3 Preclinical safety data
Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Extract:
- Lactose monohydrate
- Calcium hydrogen phosphate dihydrate
- Cellulose, powdered
- Silica, colloidal anhydrous

Tablet core:
- Cellulose, powdered
- Magnesium Stearate
- Silica, colloidal anhydrous
- Sodium starch glycolate (type A)
- Stearic acid

Film-coating:
- Eudragit E 100
- Hypromellose
- Macrogol 6000
- Talc
- Titanium dioxide E 171
- Iron oxide hydrate E 172 (= yellow iron oxide)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
The shelf life is 3 years
6.4 **Special precautions for storage**  
Do not store above 25°C.

6.5 **Nature and contents of container**  
Original packages contain 28, 30, 56, 60, 90, 120 film-coated tablets

Film-coated tablets are packed in PVC/ PVDC- aluminium blisters and inserted into a carton.

6.6 **Special precautions for disposal**  
No special requirements

7 **MARKETING AUTHORISATION HOLDER**  
Schwabe Pharma (UK) Ltd  
Alexander House  
Mere Park  
Dedmere Road  
Marlow  
Buckinghamshire  
SL7 1PD

8 **MARKETING AUTHORISATION NUMBER(S)**  
THR 23056/0011

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
27/07/2009

10 **DATE OF REVISION OF THE TEXT**  
27/07/2009
Karmamood film-coated tablets:
Patient Information Leaflet

KarmaMood® film-coated tablets
St John’s Wort extract 250mg

Please read this leaflet carefully before you start taking these tablets. It contains some important information about KarmaMood.

Keep this leaflet with the tablets. You may need to refer to it again or show it to your doctor, pharmacist or healthcare professional.

What is in this leaflet

1: What this product is and what it is used for
2: Before you take this product
3: Taking this product with other medicines
4: How to take this product
5: Side-effects
6: After taking this product
7: Product description

1: What this product is and what it is used for
This product is a traditional herbal medicinal product containing St John’s Wort. Each film-coated tablet of this product contains 250mg of extract (as dry extract) from St John’s Wort aerial parts (Hypericum perforatum L.) (3.5-6.1) equivalent to 875-1500mg of St John’s Wort. Extraction solvent: Ethanol 50% v/v.

KarmaMood® is a traditional herbal medicinal product used for the relief of slightly low mood and mild anxiety. This usage is based on traditional use only.

2: Before you take this product

DO NOT TAKE this product if:
- you are under 18 years of age
- you are pregnant or breastfeeding
- you are allergic to any of the ingredients (listed in section 7)
- you have lactose intolerance (may be affected by lactose or milk)
- your skin is exceptionally sensitive to sunlight (photosensitive)
- you are having light treatment (phototherapy) for any condition
- you are suffering from depression (see below)

Suffering from depression?

Symptoms of depression include feelings of helplessness and hopelessness, loss of interest in daily activities, appetite or weight changes, sleep changes, loss of energy and difficulty concentrating. If your doctor has told you that you are suffering from depression do not use this product. If you think that you may be suffering from depression you should tell your doctor.

Tell your doctor before using this product if you have an intolerance to some sugars (see Section 7).

While you are taking this product:
- avoid excessive sunbathing or the use of sunbeds/solariums
- stop using it 10 days prior to undergoing any surgery

Driving and operating machinery

In rare cases St John’s Wort may make you feel dizzy or sleepy. If affected do not drive or use machines.

3: Taking this product with other medicines

St John’s Wort can affect the way some medicines work and reduce their effectiveness. Medicines that can be affected by St John’s Wort include prescription medicines, and those that you may have bought yourself without a prescription.

Therefore it is important that you do not take St John’s Wort if you are using any of the medicines listed in the table opposite.
3: Taking this product with other medicines (continued)

St John’s Wort may also affect the following medicines. Therefore do not take this product with these medicines unless a doctor or pharmacist has said it is safe to do so:
- famotidine, propacetamol, sertraline, and midazolam
- morphine (endorphine analgesics)
- itraconazole, fluconazole, and telithromycin (antibiotics)
- rifampicin, amoxicillin, and metronidazole (antibiotics)
- atorvastatin and simvastatin (statins)
- risperidone (an anti-Parkinsonian medicine)
- carbamazepine (an anticonvulsant medicine)
- buspirone (an anxiolytic)
- aperient (used to treat post-operative vomiting)
- bumetanide and furosemide (diuretics)
- methylphenidate (a central nervous system or CNS stimulant)
- exenatide (a hormone agonist)
- omeprazole (a proton pump inhibitor)
- telithromycin (a bronchodilator)
- gabapentin (an antiepileptic medicine)

4: How to take this product

Adults and the elderly
Take 1 tablet daily. Swallow the tablets whole with some water or other liquid. Do not chew the tablets. Do not exceed the stated dose.

If you take too much of this product (overdose)
If you take more than the recommended dose, speak to a doctor, pharmacist or healthcare practitioner and take this leaflet with you.

If you forget to take this product
Continue to take your usual dose at the usual time, it does not matter if you have missed a dose.

If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or healthcare practitioner.

5: Side-effects

Like all medicines, this product can have side-effects. However, side-effects are uncommon with St John’s Wort. These are listed below.

Uncommon side-effects (affecting fewer than 1 in 100 people)
- digestive upset such as: indigestion, loss of appetite, nausea, diarrhoea, constipation
- fatigue
- allergic skin reactions such as rash, itching or swelling

If these persist or become troublesome, stop taking this product. These side-effects are often only temporary.

Other rare side-effects
These include headaches, nervousness or tingling (neuropathy), anxiety, dizziness, mania. Also symptoms like rashes in some users of strong ultra-violet (UV) irradiation (e.g. skin, bones) have been reported, particularly in fair-skinned individuals.

If you notice any other side-effect not mentioned above, tell your doctor or pharmacist.

6: After taking this product

You must speak to a healthcare practitioner if your symptoms worsen, if they do not improve after six weeks, or if side-effects not mentioned in this leaflet occur.

Do not use your tablets after the expiry date.
Return any out-of-date tablets to your pharmacist who will dispose of them for you. The expiry date is printed on the box and the blister pack.
Store the tablets in a cool dry place. Do not store the tablets in a place where the temperature goes above 25°C.
Keep the tablets out of the reach of children.
Keep your tablets in the blister pack until it is time to take them.

7: Product description

Each film-coated tablet of this product contains 250mg of extract (dry extract) from St John’s Wort aerial parts (Hypericum perforatum L.) (3.3-6.1) (equivalent to 875-1500mg of St John’s Wort). Each film-coated tablet contains 1mg of lactose monohydrate.

This product contains the following ingredients:
- Excipients: Lactose monohydrate, calcium hydrogen phosphate dihydrate, colloidal silicon dioxide, silicon dioxide, croscarmellose sodium.
- Table one: Cellulose, crospovidone, stearic acid, magnesium stearate.
- Filtration: E439 (E 100), hypromellose, Macrogol 6000, talc, magnesium stearate (E171), fumed silica E202 (E172) (yellow iron oxide).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

Each film-coated tablet contains 1mg of lactose monohydrate.

Each pack contains 28, 30, 60, 90 or 120 film-coated tablets. Not all pack sizes may be marketed.

Registration holder for this product
Schwabe Pharma (UK) Ltd, Alexander House, Mill Park, Buxton Road, Marlow, Bucks, SL7 1PD

Manufacturer of this product
Schwabe GmbH, Gildenstrasse 9, 49477 Bottrop, Germany

Traditional Herbal Registration number: THR 23056/0011

If you would like further information about this product, please contact: Schwabe Pharma (UK) Ltd, Alexander House, Mill Park, Buxton Road, Marlow, Bucks, SL7 1PD

Telephone: 01628 401900. Email: info@schwabe.co.uk

This leaflet was prepared in March 2009

For a large print, Braille or audio version of this leaflet, call 01628 401900

MHRA PAR; KARMAMOOD FILM-COATED TABLETS/LLOYDSPATHARMACY
ST JOHN’S WORT FILM-COATED TABLETS, THR 23056/0011
26
Lloydspharmacy St John’s wort film-coated tablets:
St John’s Wort film-coated tablets
St John’s Wort extract 250mg

Please read this leaflet carefully before you start taking these tablets. It contains some important information about Lloydspharmacy St John’s Wort.

Keep this leaflet with the tablets. You may want to read it again or show it to your doctor, pharmacist or healthcare practitioner.

What is in this leaflet
1: What this product is and what it is used for ........................................... page 1
2: Before you take this product ................................................................ page 2
3: Taking this product with other medicines ........................................ page 2-4
4: How to take this product................................................................. page 4
5: Side-effects ....................................................................................... page 5
6: After taking this product................................................................. page 6
7: Product description ............................................................................ page 6

1: What this product is and what it is used for
This product is a traditional herbal medicinal product containing St John’s Wort. Each film-coated tablet of this product contains 250mg of extract (as dry extract) from St John’s Wort aerial parts (Hypericum perforatum L.) (3.5:1) equivalent to 675-1500mg of St John’s Wort. Extraction solvent: Ethanol 60% v/v.

Lloydspharmacy St John’s Wort is a traditional herbal medicinal product used for the relief of slightly low mood and mild anxiety. This image is based on traditional use only.

2: Before you take this product
DO NOT TAKE this product if:
- you are under 18 years of age
- you are pregnant or breast-feeding
- you are lactose intolerant (react badly to lactose or milk)
- you are allergic to any of the ingredients (listed in section 7)
- your skin is exceptionally sensitive to sunlight (phototoxic)
- you are having light treatment (phototherapy) for any condition
- you are suffering from depression (see below)

Suffering from depression?
Symptoms of depression include feelings of helplessness and hopelessness, loss of interest in daily activities, appetite or weight changes, sleep changes, loss of energy and difficulty concentrating. If your doctor has told you that you are suffering from depression do not use this product. If you think that you may be suffering from depression you should tell your doctor.

Tell your doctor before using this product if you have an intolerance to some sugars (see section 7).

While you are taking this product:
- avoid excessive sunbathing or the use of sunbeds/solariums
- stop using it at least 10 days prior to undergoing any surgery

Driving and operating machinery
In rare cases St John’s Wort may make you feel dizzy or sleepy. If affected do not drive or use machines.

3: Taking this product with other medicines
St John’s Wort can affect the way some medicines work and reduce their effectiveness. Medicines that can be affected by St John’s Wort include prescription medicines, and those that you may have bought yourself without a prescription.

Therefore it is important that you do not take St John’s Wort if you are using any of the medicines listed in the table opposite.

2

Do not take this product if you are taking any of the following medicines

- All hormonal contraceptives: The birth control pill, emergency contraception, hormonal implants, creams, patches, intrauterine devices with hormones.
- All medicines for depression: Amitriptyline, clomipramine, mirtazapine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine.
- All hormonal replacement therapy (HRT) treatments: HRT tablets, patches, gels, vaginal rings.
- All medicines for thinning the blood (anticoagulants): Warfarin, acenocoumarol.
- All medicines for epilepsy: Carbamazepine, phenobarbital, phenytoin, primidone, sodium valproate.
- All immunosuppressant medicines: Cyclosporine, tacrolimus.
- All medicines for HIV infections: Amprenavir, stavudine, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, lopinavir/ritonavir, efavirenz, nevirapine, delavirdine.
- Some medicines for cholesterol: Simvastatin, atorvastatin.
- Some medicines for cancer: Iromote, dacarbazine, etoposide, irinotecan, docetaxel, irinotecan, temozolomide, mitomycin.
- Some medicines for heart disease: Digoxin, indapamide, amiodarone.
- Some medicines for migraine: Almotriptan, eletriptan, flunarizine, naratriptan, sumatriptan, zolmitriptan.
- Some medicines for high blood pressure: Amlodipine, nifedipine, felodipine, verapamil.
- A medicine for regulating mood: Lithium.
- A thyroid hormone: Thyroxine.
3: Taking this product with other medicines (continued)

St John's Wort may also affect the following medicines. Therefore do not take this product with these medicines unless a doctor or pharmacist has said it is safe to do so:
- Isotretinoin, pilocarpine, and methadone (narcotic/psychoactive medicines)
- Tramadol (an analgesic)
- Erythromycin, clarithromycin and telithromycin (antibiotics)
- Itaconazole and voriconazole (antifungals)
- Atorvastatin and itamivir/tezafuramine (antivirals)
- Imatinib (an anti-Parkinson's disease medication)
- Aspirin (an antiplatelet medication)
- Buspirone (an anxiolytic)
- Aspirin (used to treat post-operative vomiting)
- Butalbital and phenobarbital (barbiturates)
- Methylphenidate (a central nervous system or CNS stimulant)
- Exemestane (a hormone antagonist)
- Ephedrine (a bronchodilator)
- Terfenadine and promethazine (proton pump inhibitors)
- Theophylline (a bronchodilator)
- Glutathione (an antioxidant)

4: How to take this product

Adults and the elderly
Take 1 tablet daily. Swallow the tablets whole with some water or other liquid. Do not chew the tablets. Do not exceed the stated dose.

If you take too much of this product (overdose)
If you take more than the recommended dose, speak to a doctor, pharmacist or healthcare practitioner and take this leaflet with you.

If you forget to take this product
Continue to take your usual dose at the usual time. It does not matter if you have missed a dose.

If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or healthcare practitioner.

5: Side-effects

Like most medicines, this product can have side-effects. However, side-effects are uncommon with St John's Wort. These are listed below.

<table>
<thead>
<tr>
<th>Uncommon side-effects (affecting fewer than 1 in 100 people)</th>
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<tr>
<td>Digestive upset, nausea, vomiting, diarrhea, constipation</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Allergic skin reactions</td>
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</table>

Other rare side-effects
These include headaches, nausea or vomiting, diarrhoea, dizziness, flushing, dry mouth, drowsiness or tiredness. If you notice any other side-effect not mentioned above, tell your doctor or pharmacist.

6: After taking this product

You must speak to a healthcare practitioner if your symptoms worsen, if they do not improve after six weeks, or if side-effects not mentioned in this leaflet occur.

Do not use your tablets after the expiry date.

Store the tablets in a cool dry place. Do not store the tablets in a place where the temperature goes above 25°C.

Keep your tablets out of the reach of children.

Your tablets in the blister pack until it is time to take them.

7: Product description

Each film-coated tablet of this product contains 250mg of extract (as dry extract) from St John's Wort aerial parts (Hypericum perforatum L) (3.5:1) (equivalent to 875-1500mg of St John's Wort). Extraction solvent: Ethanol 60% v/v.

This product also contains the following ingredients:
- Extract: Lactose monohydrate, calcium hydrogen phosphate dihydrate, colloidal silicon dioxide, silica colloidal anhydrous.
- Tablet core: Cellulose powder, sodium starch glycolate type A, colloidal silicon dioxide, magnesium stearate.
- Film-coating: Eudragit RS 100, hypromellose, magnesium stearate, yellow iron oxide.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

Each pack contains 30 or 60 film-coated tablets. Not all pack sizes may be marketed.

Registration holder for this product
Schwabe Pharma (UK) Ltd., Alexander House, More Park, Deddridge Road, Mawley, Widnes, WA7 1PD

Manufacturer of this product
Weinhold GmbH, Gruenstrasse 23, 49477 Ibbenbueren, Germany

Traditional Herbal Registration number: THR 23056/0011

Packed for
Lloyd's Pharmacy Limited, Coventry CV2 2TX

This leaflet was prepared on 06/2009.
LABELLING

Karmamood film-coated tablets:

Blister foil:
KarmaMood® 28 tablets

NEW

KarmaMood®
St John's Wort extract 250mg
A traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety based on traditional use only

Traditionally used for: Low Mood

28 film-coated tablets

KarmaMood® is a traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety based on traditional use only.

Active ingredients: Each KarmaMood® tablet contains 250mg of extract (as dry extract) from St John's Wort (Hypericum perforatum L) (4:1) equivalent to 675±100mg of St John's Wort Extract. Inactive ingredients: Ethanol 65% v/v.

This product contains lactose monohydrate.

Dosage: For oral use. Adults and the elderly: For slightly low mood and mild anxiety take one tablet daily. The tablets should be swallowed whole with some water or other liquid.

Warning: Do not exceed the stated dose. Do not use if you:
- are under 18
- are pregnant or breast-feeding
- are allergic to any of the ingredients
- have been diagnosed with depression or you think you may be depressed
- are about to undergo surgery
- St John’s Wort products must not be taken at the same time as certain medicines including:
  - ever prescribed by your doctor
  - prescribed by your doctor (the P6)
  - when you can get without prescription

You must read the enclosed information leaflet carefully before using these tablets.

You should see a doctor or healthcare practitioner if the symptoms persist while using KarmaMood® or if side-effects occur.

Increased sensitivity of the skin to sunlight may occur in rare cases, especially in the elderly.

Keep out of sight and reach of children.

Do not store below 25°C
Store in original packaging

Manufactured in Germany
THP,invest/Schieder,Pharmas (UK) Ltd
Martins, Bursc S.L.F (IPD)
Telephone: 01423 451 180 Email info@karmamood.co.uk

Batch no:

Expiration date:

Bar Code

MHRA PAR: KARMAMOOD FILM-COATED TABLETS/LLOYDSPHARMACY
ST JOHN’S WORT FILM-COATED TABLETS, THR 23056/0011
Lloydspharmacy St John’s wort film-coated tablets:

Blister foil:

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St John’s Wort 250mg

A traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety based on traditional use only.

INSTRUCTIONS FOR USE:
For oral use. Adults and the elderly. For slightly low mood and mild anxiety take one tablet daily. The tablets should be swallowed whole with some water or other liquid.

WARNING: DO NOT EXCEED THE STATED DOSE.
DO NOT USE IF YOU:
- are under 18 years
- are pregnant or breast-feeding
- are allergic to any of the ingredients
- have been diagnosed with depression or you think you may be depressed
- are about to undergo surgery

St John’s Wort products must not be taken at the same time as certain medicines including:
- other prescribed by your doctor
- hormonal contraceptives (including the pill)

Some you can get without prescription;
KEEP MEDICINES OUT OF SIGHT AND REACH OF CHILDREN

You must read the enclosed information leaflet carefully before taking these tablets.

You should see a doctor or healthcare practitioner if the symptoms persist whilst using St John’s Wort or if side-effects not mentioned in the patient information leaflet occur.
Increased sensitivity of the skin to sunlight may occur in rare cases, especially in fair-skinned people.

STORAGE:
Do not store above 25°C.
Store in the original packaging.

ACTIVE INGREDIENTS:
Each tablet contains 250mg of extract (as dry extract) from St John’s Wort (hypericum perforatum L.) (5.6-8.11), equivalent to 870-1300mg of St John’s Wort. Extraction solvent: ethanol 60% v/v.

B/N:

EXP: