DiaFemin Tablets

THR 33518/0028

UKPAR

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DIAFEMIN TABLETS

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Diapharm Regulatory Services GmbH a Traditional Herbal Registration Certificate for the traditional herbal medicinal product DiaFemin Tablets (Traditional Herbal Registration number: THR 33518/0028) on 12 April 2011. This product is available without prescription and can be bought from pharmacies and other outlets.

DiaFemin Tablets is a traditional herbal medicinal product used for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety based on traditional use only. The active ingredients of DiaFemin Tablets come from St John’s wort (Hypericum perforatum L.) aerial parts and Black cohosh (Cimicifuga racemosa L. Nutt.) rhizome and root.

This registration is based exclusively upon the longstanding use of St. John’s wort aerial parts and Black cohosh rhizome and root as traditional herbal medicines and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration scheme to prove scientifically that a 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.
DIAFEMIN TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicine DiaFemin Tablets (THR 33518/0028) to Diapharm Regulatory Services GmbH on 12 April 2011. This product is on the general sales list (GSL).

This application was submitted according to Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme. The product is used for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety, based on traditional use only.

The data supplied by the applicant demonstrate 30 years of traditional use of St John’s wort and Black cohosh, including at least 15 years of use in the European Community. A satisfactory review of the available safety data on St John’s wort and Black cohosh has also been provided, together with an Expert Safety Report supporting the proposed product.
**PHARMACEUTICAL ASSESSMENT**

**HERBAL SUBSTANCE:**  
**ST JOHN’S WORT**

*Scientific name of the plant:* Hypericum perforatum L.  
*Family:* Hypericaceae (syn. Guttiferae)  
*Synonyms of the herbal substance:* St. John’s wort

The St John’s wort plants used in this product are sourced from Europe or North America between spring and summer and from South America or Africa from November to January. The plants are either cultivated or collected from the wild. The aerial parts are harvested or collected during the plant’s flowering period. After harvest or collection the herb is dried quickly under mild conditions.

Confirmation has been provided that the herbal substance is produced in line with the Guideline on Good Agricultural and Collection Practice (GACP) EMEA/HMPC/246816/2005 and that the herbal substance has not been fumigated or treated with ionizing radiation during growing or storage. During cultivation crops are treated with fertiliser, herbicide and fungicide, but insecticides are not used.

**Control of Herbal Substance**
An appropriate specification based on the Ph Eur monograph is applied and is acceptable. The specification is supported by the batch data provided.

**Container Closure System**
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Confirmation is given that the herbal substance will be tested prior to being used to make the herbal preparation. A shelf-life for the herbal substance is not appropriate because it is only a precursor of the active substance, the herbal preparation. The actual guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance.

**HERBAL PREPARATION:**  
**ST JOHN’S WORT DRY EXTRACT**

*Parts of the plant used:* Dried entire or comminuted aerial parts, collected shortly before or during the blossoming period  
*Ratio of the herbal substance to the herbal preparation (native):* 3.5-6:1  
*Extraction solvent:* Ethanol 60 % m/m
**Manufacture**
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram has been provided. The in-process controls are satisfactorily detailed. There are no critical steps identified as the manufacture of the herbal preparation is considered a standard procedure.

Certificates of analysis for all materials used in the manufacture of the herbal preparation have been provided.

**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.

**Container Closure System**
Confirmation is provided that all components of the container closure system used to store this herbal preparation comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Stability studies have been performed in accordance with current guidelines. The proposed re-test period for the St. John’s wort dry extract is acceptable.

**HERBAL SUBSTANCE:** BLACK COHOSH

**Scientific name of the plant:** Cimicifuga racemosa L. Nutt
**Family:** Ranunculaceae
**Synonyms of the herbal substance:** Cimicifuga, Black snakeroot, Actaea racemosa

The Black cohosh plants used in this product are collected from the wild, mainly in the USA. The rhizome and the attached roots are collected during the plant’s flowering period. These are dried under natural conditions in covered and well ventilated places.

Confirmation has been provided that the herbal substance is produced in line with the Guideline on Good Agricultural and Collection Practice (GACP) EMEA/HMPC/246816/2005 and that the herbal substance has not been fumigated or treated with ionizing radiation.
Control of Herbal Substance
An appropriate specification based on the draft Ph Eur monograph is applied and is acceptable. The specification is supported by the batch data provided.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
Confirmation is given that the herbal substance will be tested prior to being used to make the herbal preparation. A shelf-life for the herbal substance is not appropriate because it is only a precursor of the active substance, the herbal preparation. The actual guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance.

HERBAL PREPARATION: BLACK COHOSH DRY EXTRACT

Parts of the plant used: Rhizome with the attached roots
Ratio of the herbal substance to the herbal preparation (native): 4.5 - 8.5: 1
Extraction solvent: Ethanol 60 % (V/V)

Manufacture
A satisfactory description of the manufacturing process of the herbal substance and flow diagram has been provided. The in-process controls are satisfactorily detailed. There are no critical steps identified as the manufacture of the herbal preparation is considered a standard procedure.

Certificates of analysis for all materials used in the manufacture of the herbal preparation have been provided.

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.

Container Closure System
Confirmation is provided that all components of the container closure system used to store the herbal preparation comply with Directive 2008/39/EC relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Stability studies have been performed in accordance with current guidelines. The proposed re-test period for the Black cohosh dry extract is acceptable.

**HERBAL PRODUCT: DIAFEMIN TABLETS**

**Description and Composition of the Herbal Product**
DiaFemin Tablets are light yellow coated tablets, shape like lenses, with a smooth glossy surface. Each tablet contains 300 mg of dry extract from St. John’s wort aerial parts and 6.4 mg of dry extract from Black cohosh rhizome and root. The rest of the tablet is composed of maltodextrin, silica (colloidal anhydrous), cellulose (powdered), lactose monohydrate, croscarmellose sodium, cellulose (microcrystalline), sodium starch glycollate (type A), magnesium stearate, hypromellose, sucrose, talcum, calcium carbonate (E 170), tragacanth, acacia, liquid glucose (dry substance), titanium dioxide (E 171), iron oxide hydrate (E 172), vanillin, beeswax (white), carnauba wax and shellac.

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients are controlled in line with their respective Ph Eur monograph, with the exception of iron oxide hydrate, which complies with Directive 95/45/EC relating to colouring agents allowed for use in medicinal products and Directive 2001/50/EC; in the absence of an appropriate Ph Eur monograph for this excipient this is acceptable.

The magnesium stearate used in the product is confirmed to be of vegetable origin and the lactose monohydrate is sourced from milk from animals suitable for human consumption in accordance with current requirements.

**Manufacture**
A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches and the results are satisfactory.

**Control of Herbal Product**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.
**Container Closure System**
The tablets are sealed into binary blisters made of PVC/PVDC-aluminium that are inserted into a carton. Each carton contains 30, 60, 90 or 100 tablets. Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with Directive 2002/72/EC.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 3 years is appropriate when the storage precautions ‘Do not store above 25° C’ and ‘Store in the original package’ are applied.

**Pharmaceutical Expert**
The Quality Overall Summary has been written by a pharmacist with extensive experience with herbal products.

**Assessor’s comments on the Summary of Product Characteristics, label and Patient Information Leaflet**
All product literature is satisfactory.

A package leaflet has 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 leaflet is 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 it contains.

**Assessor’s overall conclusions on quality**
The grant of a Traditional Herbal Registration is acceptable.
NON-CLINICAL ASSESSMENT

NON-CLINICAL ASPECTS
The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of St John’s wort aerial parts and Black cohosh rhizome and root.

NON-CLINICAL OVERVIEW
The applicant has submitted a literature review with this application. An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a suitably qualified professional.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on St John’s wort aerial parts and Black cohosh rhizome and root it is not possible to assess if the safety package for the phytochemical constituents of these active ingredients 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.

Assurance was provided that the results of genotoxicity testing will be provided before renewal of the registration.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC for this product is satisfactory from a non-clinical 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
There are no objections to granting of a Traditional Herbal Registration from a non-clinical point of view.
CLINICAL ASSESSMENT

PROPOSED INDICATION
The applicant has submitted the following therapeutic indication:

“A traditional herbal medicinal product used for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety based on traditional use only.”

The indication is acceptable.

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

“For oral use only. For women experiencing menopausal symptoms, take 1 tablet daily. Tablets should be taken at the same time of day if possible (morning or evening) and swallowed whole with plenty of liquid. Do not chew the tablets.

If symptoms worsen or do not improve after 6 weeks a doctor or qualified healthcare practitioner should be consulted.

The use in children or adolescents under 18 years of age is not recommended (see Section 4.4 special warnings and precautions for use).”

This is acceptable.

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

EVIDENCE OF TRADITIONAL USE
St John’s wort aerial parts and Black cohosh rhizome and root are generally accepted to have a tradition of use as herbal medicines. 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 EU.

The applicant has provided a bibliographic review which shows evidence for the medicinal use of St John’s wort aerial parts and Black cohosh rhizome and root for more than 30 years, including at least 15 years within the EU. Therefore, there is sufficient evidence of traditional use of these herbal preparations and a traditional herbal registration can be granted.

SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliography of the safety data together with an expert report. The safety review has been provided, as well as an expert report written by a professional with relevant expertise. A CV has been included. The applicant has provided satisfactory information supporting the safety of St John’s wort aerial parts and Black cohosh rhizome and root.

In addition, the Committee on Herbal Medicinal Products (HMPC) assessment report for St John’s wort aerial parts covers the non-clinical and clinical safety issues associated with this herb.

**PRODUCT LITERATURE**
The SmPC, PIL and labelling for this product are medically satisfactory.

**RECOMMENDATIONS**
A Traditional Herbal Registration may be granted.
OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

NON-ClinICAL
No new non-clinical data were submitted with this application. However, assurance was provided that the results of genotoxicity testing will be provided before renewal of this registration. This is satisfactory.

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 aerial parts and Black cohosh rhizome and root for a period exceeding 30 years, including at least 15 years within the EU.

A satisfactory review of the safety data has been provided. In addition, the Committee on Herbal Medicinal Products (HMPC) assessment report for St John’s wort aerial parts covers the non-clinical and clinical safety issues associated with this herb.

The SmPC, PIL and labelling are satisfactory.

RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The risk: benefit balance is acceptable and a Traditional Herbal Registration may be granted.
### DIAFEMIN TABLETS

#### THR 33518/0028

#### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Traditional Herbal Registration application on 1 March 2011</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 8 April 2011</td>
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<tr>
<td>3</td>
<td>A THR was granted on 12 April 2011</td>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
DiaFemin Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each coated tablet contains:

300 mg of extract (as dry extract) from St. John’s Wort aerial parts
(Hypericum perforatum L.) (3.5-6:1) (equivalent to 1050 – 1800 mg of St.
John’s Wort).
Extraction solvent: Ethanol 60% m/m

and

6.4 mg of extract (as dry extract) from Black Cohosh rhizome and root
(Cimicifuga racemosa (L.) Nutt.) (4.5-8.5:1) (equivalent to 28.80-54.40 mg of
Black Cohosh rhizome).
Extraction solvent: Ethanol 60% v/v

Each coated tablet contains 19 mg of lactose monohydrate, 234 mg of sucrose
and 6 mg of glucose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Coated tablet.
Light yellow, shape like lenses, smooth glossy surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
A traditional herbal medicinal product used for the relief of symptoms of the
menopause, including hot flushes, night sweats, slightly low mood and mild
anxiety based on traditional use only.

4.2 Posology and method of administration
For oral use only.
For women experiencing menopausal symptoms, take 1 tablet daily. Tablets
should be taken at the same time of day if possible (morning or evening) and
swallowed whole with plenty of liquid. Do not chew the tablets.

If symptoms worsen or do not improve after 6 weeks a doctor or qualified
healthcare practitioner should be consulted.
The use in children or adolescents under 18 years of age is not recommended (see Section 4.4 special warnings and precautions for use).

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

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, CYP2C19 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 medicine.

Patients who have hepatic and/or renal impairment since the safety of Black cohosh extract has not been studied in patients with hepatic and/or renal impairment.

In patients who have active liver disease or a history of liver damage.

In patients currently receiving treatment for or has had a history of an oestrogen dependent tumour.

As there is evidence that Black cohosh may have hormone-like actions, it should only be used by women of childbearing potential if contraception is used.

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 a doctor or qualified healthcare practitioner should be consulted.

The use of this product in children and adolescents under 18 years of age is not recommended since there is no relevant use.

This product is intended for relief of menopausal symptoms including slightly low mood and mild anxiety. Patients with signs and symptoms of depression should consult a doctor 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).

There have been rare cases of hepatic reactions associated with the use of Black Cohosh. Patients taking DiaFemin Tablets should be informed to immediately stop the use of the product and consult their doctor if they develop signs and symptoms suggestive of liver dysfunction. (Fatigue, anorexia, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).

Advice should be sought from a doctor if the patient has a family history of an oestrogen dependent tumour.

Oestrogens may only be taken simultaneously with DiaFemin Tablets under supervision of a doctor, as their effect may be intensified by Black Cohosh.

If menstrual disorders occur or menstruation re-appears and if the symptoms are persistent, of unknown origin, or have recently occurred, a doctor should be consulted as this may indicate the presence of other conditions which need to be medically diagnosed.

Patients with rare hereditary problems of galactose intolerance and/or fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This product contains sucrose, lactose and glucose.

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, CYP2C19 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.

The concomitant use of ciclosporin, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors, irinotecan and warfarin is contraindicated.

Special care should be taken in the case of concomitant use of all drug substances the metabolism of which is influenced by CYP1A2, CYP3A4, CYP2C9, CYP2C19 or P-glycoprotein (e.g. amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, digoxin, finasteride) because a reduction of plasma concentration is possible.

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>
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<tbody>
<tr>
<td><strong>Anaesthetics /pre-operative medicines</strong></td>
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<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>
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<tr>
<td><strong>Analgesics</strong></td>
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<tr>
<td>Tramadol</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>Antianginals</strong></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>
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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>
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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>
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<tr>
<td><strong>Anticoagulants</strong></td>
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<tr>
<td>warfarin, acenocoumarol</td>
<td>Reduced anticoagulant effect and need for increased dose</td>
<td>Do not take with this product.</td>
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<td><strong>Antidepressants</strong></td>
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<tr>
<td>Tricyclics eg. amitriptyline, clomipramine</td>
<td>Increased serotonergic effects with increased incidence of adverse reactions.</td>
<td>Do not take with this product.</td>
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<td>MAOIs eg. moclobemide</td>
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<td>SSRIs eg. citalopram, escitalopram, fluoxetine, fluvoxamine,</td>
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<tr>
<td>Category</td>
<td>Interaction</td>
<td>Warning</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>paroxetine, sertraline,</td>
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<tr>
<td>Others eg.</td>
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<tr>
<td>duloxetine, venlafaxine</td>
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<tr>
<td><strong>Antiepileptics</strong></td>
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<tr>
<td>All drugs in this class</td>
<td>Reduced blood levels with increased risk of frequency and severity of seizures.</td>
<td>Do not take with this product.</td>
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<tr>
<td>including:</td>
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<tr>
<td>carbamazepine</td>
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<td>phenobarbitone</td>
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<td>phenytoin</td>
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<td>primidone</td>
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<tr>
<td>sodium valproate</td>
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<tr>
<td><strong>Antifungals</strong></td>
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<tr>
<td>itraconazole, voriconazole</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
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<tr>
<td>artemether</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>lumefantrine</td>
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<tr>
<td><strong>Anti-parkinsons</strong></td>
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<tr>
<td>rasagiline</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>Antipsychotics</strong></td>
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<tr>
<td>aripiprazole</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>Antivirals</strong></td>
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<tr>
<td>HIV protease inhibitors:</td>
<td>Reduced blood levels with possible loss of HIV suppression.</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td>amprenavir, atazanavir,</td>
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<tr>
<td>darunavir, fosamprenavir,</td>
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<td>indinavir, lopinavir,</td>
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<td>nelfinavir, ritonavir,</td>
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<td></td>
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<tr>
<td>saquinavir, tipranavir</td>
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<tr>
<td>HIV non-nucleoside</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reverse transcriptase</td>
<td>Reduced blood levels with possible loss of HIV suppression</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td>inhibitors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>efavirenz, nevirapine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>delavirdine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anxiolytics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>buspirone</td>
<td>Increased serotonergic</td>
<td>Do not take with this product.</td>
</tr>
<tr>
<td>Drug Type</td>
<td>Other Drugs</td>
<td>Effect Description</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>Reduced blood and loss of control of heart rhythm or heart failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>CNS Stimulants</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>Reduced blood levels with risk of unintended pregnancy and breakthrough bleeding.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
<tr>
<td>Hormone antagonists</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not take with this product.</td>
<td></td>
</tr>
</tbody>
</table>
### Diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>eplerenone</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### 5HT agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan</td>
<td>Increased serotonergic effects with increased incidence of adverse reactions.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Imunosuppressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciclosporin, tacrolimus</td>
<td>Reduced blood levels with risk of transplant rejection.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Lipid regulating drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>simvastatin, atorvastatin</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Lithium

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

### Proton pump inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>lansoprazole, omeprazole</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Theophylline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced blood levels and loss of control of asthma or chronic airflow limitation.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Thyroid hormones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>thyroxine</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### Oral hypoglycaemic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>gliclazide</td>
<td>Reduced blood levels with risk of therapeutic failure.</td>
<td>Do not take with this product.</td>
</tr>
</tbody>
</table>

### 4.6 Pregnancy and lactation

The safety of this product during pregnancy and lactation has not been established. Therefore it should be avoided during pregnancy or lactation. Additionally because of the potential for Black cohosh to have hormone-like actions, the use by women who could become pregnant is not recommended unless contraception is used.

### 4.7 Effects on ability to drive and use machines

May impair the ability to drive and use machines. If affected, do not drive or operate machines.

### 4.8 Undesirable effects

Gastrointestinal disorder (e.g. dyspepsia, anorexia, nausea, diarrhoea, constipation); allergic skin reaction (e.g. rash, urticaria, pruritis); fatigue and restlessness may occur. The frequency is not known.
Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight or strong ultra-violet (UV) irradiation.
Other ADRs reported in the literature with products containing Black cohosh include facial oedema, peripheral oedema and weight gain.
Other ADRs reported in the literature with products containing St. John’s wort include headaches, neuropathy, anxiety, dizziness and mania.
In rare cases, Black cohosh containing products may cause liver reactions (including hepatitis, jaundice and disturbances in liver function tests).
If other adverse reactions not mentioned above occur, a doctor or qualified healthcare practitioner should be consulted.

4.9 Overdose
There are no data on human overdose with St John’s Wort.
After intake of up to 4.5 g dry extract per day for 2 weeks and additionally 15 g dry extract just before hospitalization, seizures and confusion have been reported.
Where a large overdose has occurred, phototoxic reactions may occur. The skin of the patient should be protected for one to two weeks from UV irradiation and sunlight. 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.

Older herbal texts state that doses of over 5 g of unprocessed Black Cohosh daily may produce symptoms of nausea, vomiting, dizziness, visual and nervous disturbances, reduced pulse rate and increased perspiration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Not required as per Article 16 c (1) (a) (iii) of Directive 2001/83/EC as amended.

5.2 Pharmacokinetic properties
Not required as per Article 16 c (1) (a) (iii) of Directive 2001/83/EC as amended.

5.3 Preclinical safety data
The preclinical toxicology data available are limited. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Extract excipients:
Maltodextrin
Silica, colloidal anhydrous
Cellulose, powdered
Lactose monohydrate

**Tablet core:**
- Silica, colloidal anhydrous
- Croscarmellose sodium
- Cellulose, microcrystalline
- Sodium starch glycollate (type A)
- Magnesium stearate

**Excipients of the coating:**
- Hypromellose
- Sucrose
- Talcum
- Calcium carbonate E 170
- Tragacanth
- Acacia
- Liquid glucose (dry substance)
- Titanium dioxide E 171
- Iron oxide hydrate E 172
- Vanillin
- Beeswax, white
- Carnauba wax
- Shellac

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years

6.4 **Special precautions for storage**
Do not store above 25° C. Store in the original package.

6.5 **Nature and contents of container**
Original packages contain 30, 60, 90 or 100 coated tablets

DiaFemin 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**
Diapharm Regulatoy Services GmbH
Würzburger Str. 3
26121 Oldenburg
Germany
8 MARKETING AUTHORISATION NUMBER(S)
THR 33518/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
12/04/2011

10 DATE OF REVISION OF THE TEXT
12/04/2011
DiaFemin Tablets
St. John's Wort extract 300 mg and Black Cohosh root extract 6.4 mg

Please read this leaflet carefully before you start taking these tablets.
• It contains some important information about DiaFemin tablets.
• Keep this leaflet with the tablets.
• You may want to read it again or show it to your doctor, pharmacist or qualified healthcare practitioners.

What is in this leaflet
1. What this product is and what it is used for
2. Before you take this product
3. How to take this product
4. Possible side-effects
5. How to store this product
6. Further information

What is in this leaflet

1. What this product is and what it is used for
This product is a traditional herbal medicinal product containing extracts of:
• St. John's Wort
• Black Cohosh root
For full details see section 6.
DiaFemin Tablets is a traditional herbal medicinal product used for the relief of symptoms of the menopause, including hot flashes, night sweats, slightly low mood and mood swings, based on traditional use only.
As there is evidence that Black cohosh may have hormone-like actions, this product should only be used by women of childbearing potential if contraception is used.

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 child-bearing potential and do not use adequate contraception
• you are allergic to any of the ingredients (see section 6)
• your skin is exceptionally sensitive to sunlight (photo-sensitivity)
• you are having light treatment (phototherapy) for any condition
• you are suffering from depression (see below)
• you have ever had or are suffering from liver disease (e.g. hepatitis, jaundice or cirrhosis)
• you have ever had or are suffering from an oestrogen dependent tumour
Tell your doctor before using this product if you:
• are currently taking any medicines containing oestrogens
• think you may be suffering from depression (see below)
• have a personal history of mental health problems
• have been told by your doctor that you have an intolerance to some sugars. This product contains lactose monohydrate, sucrose and glucose (see section 6).

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

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. Even though you may be suffering from depression you should tell your doctor.

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 machinery.

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 prescription. Therefore, it is important that you do not take this product if you are using any of the medicines listed in the table.

Do not take this product if you are taking any of the following medicines:
All hormonal contraceptives
• The birth control pill, injectable, implantable, ring, vaginal suppository, transdermal patches with hormones.
All medicines for depression/anxiety
• Antidepressants, anxiolytics, mood stabilizers, dexamphetamine, haloperidol, mianserin, mirtazapine, paroxetine, perphenazine, prazepam, phenelzine, venlafaxine.
All hormonal replacement therapy
• 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 benzodiazepines
• Chlorazepate, diazepam
All medicines for HIV infections
• protease inhibitors, reverse transcriptase inhibitors, integrase inhibitors, immune suppressives.
Some medicines for choliodal pain
• Simvastatin, atorvastatin
Some medicines for cancer
• Methotrexate, dacarbazine, etoposide, ifosfamide, ketomycine, melphalan, mitomycin, vincristine, vinblastine, dacarbazine, ifosfamide, mitomycin, vincristine, vinblastine, dacarbazine, ifosfamide, mitomycin, vincristine, vinblastine.
Some medicines for heart disease
• Digoxin, lansoprazole, amiodarone
Some medicines for migraines
• Aminophylline, cromolyn, aspirin, ibuprofen, ketorolac, paracetamol, naproxen, ibuprofen, ketorolac, paracetamol, naproxen.
Some medicines for high blood pressure
• Amlodipine, enalapril, verapamil, felodipine
A medicine for regulating mood
• Lithium
A thyroid hormone
• Thyroxine
MHRA PAR; DIAFEMIN TABLETS, THR 33518/0028

3: How to take this product

Adults and the elderly
Take 1 tablet daily. The tablet should be taken at the same time each day. Swallow the tablet whole with a little liquid. Do not chew the tablet.

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 qualified healthcare professional 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, ask your doctor, pharmacist, or qualified healthcare professional.

After taking this product
You must speak to a doctor or qualified healthcare professional if your symptoms worsen, if they do not improve after six weeks, or if you notice any side effects or changes in your menstrual bleeding.

4: Possible side effects

Like all medicines, this product can have side effects. Some are listed below.

- Gastrointestinal disorders e.g. indigestion, nausea, diarrhoea, constipation
- Fatigue and tiredness
- Headache
- breast enlargement
- injection site reactions, such as redness, swelling, itching or easier bruising
- weight gain
- Skin and skin disorders: rash itching of the skin, blisters

If these side effects or any of those listed in Special warnings and precautions for use, continue to occur, or if these side effects get better but are still present, stop taking this product immediately and consult your doctor.

Other side effects

These include headaches, nervousness, tiredness, dizziness, weakness, and changes in appetite or weight. These side effects are not usually serious, but if they become serious, tell your doctor or pharmacist.

5: How to store this product

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. Store them in the original packaging.

Keep the tablets out of the reach of children.

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

6: Further information

Each coated tablet of this product contains 200 mg of extract (as dry extract) from St. John's Wort, paroxetine hydrochloride (equivalent to 200 mg of St. John's Wort) and diazepam (equivalent to 10 mg of diazepam). Each coated tablet contains the following excipients: Lactose monohydrate; corn starch; croscarmellose sodium; pregelatinised starch; magnesium stearate; hydroxypropylcellulose; colloidal silicon dioxide; hypromellose; sodium starch glycolate; titanium dioxide Q.S.; and gelatin. Coating: Hypromellose, sucrose, talc, calcium carbonate E 170, magnesium stearate, yellow iron oxide, red iron oxide, yellow iron oxide, black iron oxide, patent red. If you have been told by your doctor that you have an intolerance to any of these, contact your doctor before taking this product. Each coated tablet contains 10 mg of diazepam and 200 mg of extract from St. John's Wort. Each pack contains 26, 60, 90, or 100 coated tablets. Not all pack sizes may be marketed.

The marketing authorisation holder of this product is Diapharm Regulatory Services GmbH, Woelfinger Str. 5, 33403 Oededeck, Germany. Traditional herbal registration number: THR 33518/0028.

If you would like further information about this product, please contact:

Diapharm Regulatory Services GmbH, Woelfinger Str. 5, 33403 Oededeck, Germany. Telephone: +49 (0) 5441-965000, E-mail: info@diapharm.de

This leaflet was prepared in November 2021.

You can help to make medicines safer by reporting any side effects to the Yellow Card Scheme at www.yellowcard.gov.uk. Alternatively you can post a paper Yellow Card form from your GP's surgery or pharmacy, or call 0800 206 726 (available Mon-Fri 9am-5pm).
LABELLING

Blister:
Carton: