

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pacifa Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 425 mg of extract (as dry extract) from *Hypericum perforatum* L., herba (St. John's Wort) (3.5-6 : 1), corresponding to: 0.5-1.4 mg of total hypericins; 25.5-89.1 mg of flavonoids, expressed as rutin; maximum 23.6 mg of hyperforin.

Extraction solvent: ethanol 60% m/m.

Excipients with known effect:

Each tablet contains 0.07 mg of sodium, 234 mg of sucrose and 6 mg of glucose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Yellow, coated tablet, shape like lenses, free from ruptures.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pacifa is indicated for the short term treatment of mild depressive symptoms.

4.2 Posology and method of administration

For oral short term use only.

Adults and the elderly

One coated tablet once or twice a day. Coated tablets should be swallowed with some liquid.

Children and adolescents (<18 years)

Pacifa should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

If the condition worsens or if symptoms persist for more than 4 weeks medical advice should be sought. As with other antidepressants in general, an anti-depressive effect is not expected before 14 days of treatment, however if a treatment response is not apparent within 4 weeks or symptoms worsen during use a doctor should be consulted.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients (See sections 4.4 & 6.1)

- Pregnancy and Lactation
- Pacifa should not be used in patients with known dermal photosensitivity or those undergoing phototherapy any photodiagnostic procedures or intense UV exposure.

- Pacifa should not be taken concomitantly with any of the medicines specified 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 the transport protein P-glycoprotein. This results in pharmacokinetic interactions with a large number of medicines including a possible decrease in the effectiveness of those medicines.
- Patients who have undergone transplant surgery and are taking immunosuppressant medication should not take Pacifa.
- 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 serotonergic effects associated with these interactions this product should not be used concomitantly with these types of medicines (see section 4.5).

4.4 Special warnings and precautions for use

- Do not exceed the stated dose.
- Women of child-bearing potential and contraceptive measures: St John's Wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. Intracyclic menstrual bleeding may also occur. This applies to all hormonal contraceptives: - the oral contraceptive pill, emergency contraceptive pill, hormonal implants/injections; hormonal patches/ creams. Women using hormonal contraceptives for pregnancy prevention should use additional contraceptive measures. There are currently no data on interaction with hormonal intrauterine devices but this warning should also be taken into consideration when using hormonal intrauterine devices (See section 4.5 and 4.6).
- The use of Pacifa is not recommended for children and adolescents under 18 years of age, because the data are not sufficient and medical advice should be sought.
- Pacifa is indicated for the short term treatment of mild depressive symptoms, if these symptoms worsen during use of Pacifa or persist for more than 4 weeks a doctor should be consulted.
- Suicide/suicidal thoughts or clinical worsening: Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
- Pacifa should be used with caution in patients with a history of mania/hypomania or psychosis.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase in sufficiency should not take this medicine.
- In very rare cases, particularly in fair-skinned individuals, sunburn type reactions may occur on skin areas exposed to strong sunlight due to photosensitisation by St. John's Wort (*Hypericum perforatum*). Patients taking Pacifa should avoid excessive sunbathing or the use of sunbeds or solariums.
- Pacifa should be discontinued at least 10 days prior to elective surgery due to the potential for St. John's Wort (*Hypericum perforatum*) to interact with drugs used during general and regional anaesthesia. After cessation the raised enzyme activity returns to normal within one week.

4.5 Interaction with other medicinal products and other forms of interaction

Evidence shows that St John’s Wort (*Hypericum perforatum*) interacts with medicines, either by affecting drug metabolism or levels of neurotransmitters.

Substances in St John’s Wort (*Hypericum perforatum*) have been shown to induce 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. When patients stop taking St John’s Wort preparations, blood levels of interacting medicines may rise, leading to toxicity

The concomitant use of certain medications is contraindicated. These include but are not limited to: ciclosporin, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors, irinotecan and warfarin. Please see table below for full list of contraindicated medications.

In addition to the interactions already identified, special care should be taken in case of concomitant use of all drug substances the metabolism of which is influenced by CYP1A2, CYP2C9, CYP2C19, CYP3A4 or P - glycoprotein (e.g. fexofenadine, zolpidem), because a reduction of plasma concentration is possible.

St John’s Wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. Intracyclic menstrual bleeding may also occur. This applies to all hormonal contraceptives. There are currently no data on concomitant use of St John’s Wort with hormonal intrauterine devices. Women using hormonal contraceptives for pregnancy prevention should use additional contraceptive measures (see section 4.4 and 4.6).

All antiepileptic medication may interact with St John’s Wort and therefore should not be taken concomitantly with Pacifa.

Clinically significant pharmacodynamic interactions have also been identified with the SSRI antidepressants, buspirone and the triptan group of medicines used to treat migraines. Due to the increased risk of serious adverse reactions from the serotonergic effects associated with these interactions Pacifa (St John’s Wort) should not be used concomitantly with these types of medicines.

Pacifa (St John’s Wort) should not be taken concomitantly with the medicines included in the following table:

CO-ADMINISTERED DRUG	INTERACTION	RECOMMENDATIONS CONCERNING ADMINISTRATION
Anaesthetic/pre-operative medicines		
Fentanyl, propofol, sevoflurane, benzodiazepines e.g midazolam	Reduced blood levels with risk of therapeutic failure.	Based on the elimination half-lives of hypericum and hyperforin this product should be discontinued at least 10 days prior to surgery.
Analgesics		
Tramadol, methadone, oxycodone	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Antianginals		
Ivabradine	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Anti-arrhythmics		
Amiodarone	Reduced blood levels with risk of	Do not take with this product.

	therapeutic failure.	
Antibacterials		
Erythromycin, clarithromycin, telithromycin	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Anticoagulants		
Warfarin, acenocoumarol clopidogrel dabigatran rivaroxaban	Reduced anticoagulant effect and need for increased dose.	Do not take with this product.
Antidepressants		
Tricyclics eg: amitriptyline, clomipramine MAOIs eg Moclobemide SSRIs citalopram escitalopram fluoxetine fluvoxamine paroxetine sertraline Others eg duloxetine venlafaxine, bupropion	Increased serotonergic effects with increased incidence of adverse reactions.	Do not take with this product.
Mood Stabilisers		
Lithium	Reduced blood levels with a risk of therapeutic failure.	Do not take with this product.
Antiepileptics		
All drugs in this class including: carbamazepine phenobarbitone phenytoin primidone sodium valproate	Reduced blood levels with increased risk of frequency and severity of seizures.	Do not take with this product.
Antifungals		
Itraconazole Voriconazole	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Antimalarials		
Artemether Lumefantrine	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Anti-parkinsons		
Rasagiline	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Antipsychotics		
Aripiprazole	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Antivirals		
HIV protease inhibitors: Amprenavir; atazanavir; darunavir fosamprenavir indinavir lopinavir nelfinavir ritonavir saquinavir tipranavir	Reduced blood levels with possible loss of HIV suppression.	Do not take with this product.
HIV non-nucleoside reverse transcriptase inhibitors:	Reduced blood levels with possible loss of HIV	Do not take with this product.

efavirenz; nevirapine delavirdine	suppression.	
Antiandrogen		
Finasteride	Reduced blood levels with risk of therapeutic failure	Do not take with this product.
Anxiolytics		
Benzodiazepines	Reduced blood levels with risk of therapeutic failure	Do not take with this product.
Buspirone	Increased serotonergic effects with increased incidence of adverse reactions.	Do not take with this product.
Antiemetic		
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		
Methyl phenidate	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
Cytotoxics		
Irinotecan, dasatinib, erlotinib, imatinib, sorafenib, sunitinib, etoposide, mitotane, docetaxel	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 Intrauterine devices with hormones	Reduced blood levels with a risk of unintended pregnancy and breakthrough bleeding.	Do not take with this product.
Hormone Replacement Therapy		

Hormone replacement therapy: oral transdermal patches, gels vaginal rings	Reduced blood levels with risk of therapeutic failure.	Do not take with this product.
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		
Alomriptan eletriptan frovatriptan naratriptan rizatriptan sumatriptan and zolmitriptan	Increased serotonergic effects with increased incidence of adverse reactions.	Do not take with this product.
Immunosuppressants		
Ciclosporin tacrolimus	Reduced blood levels with a risk of transplant rejection	Do not take with this product.
Lipid regulating drugs		
Simvastatin atorvastatin	Reduced blood levels with a risk of therapeutic failure.	Do not take with this product.
Proton pump inhibitors		
Lansoprazole omeprazole	Reduced blood levels with a risk of therapeutic failure.	Do not take with this product.
Thyroid hormones		
Thyroxine	Reduced blood levels with a risk of therapeutic failure.	Do not take with this product.
Oral hypoglycaemic drugs		
Gliclazide	Reduced blood levels with a risk of therapeutic failure.	Do not take with this product.
Xanthines		
Theophylline	Reduced blood levels and loss of control of asthma or chronic airflow limitation.	Do not take with this product

4.6 Fertility, pregnancy and lactation

The safety of St John’s Wort during pregnancy and lactation has not been established. Animal studies have shown equivocal results with regard to reproductive toxicity, with some data suggesting that hypericin one of the active components of St John’s Wort may have teratogenic effects. In the absence of sufficient data, use of Pacifa during pregnancy and lactation should be avoided.

Fertility:

No data available

Women of child-bearing potential and contraceptive measures

St John’s Wort may reduce blood levels of hormonal contraceptives resulting in a risk of unintended pregnancy and breakthrough bleeding. Women using hormonal contraceptives for pregnancy prevention should use additional contraceptive measures.

This applies to all hormonal contraceptives:- the oral contraceptive pill, emergency contraceptive pill, hormonal implants/injections; hormonal patches/ creams. There are currently no data on interaction with hormonal intrauterine devices but this warning should also be taken into consideration when using hormonal intrauterine devices (see section 4.4 and 4.5).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Very common (>1/10)

Common (>1/100, <1/10)

Uncommon (>1/1,000, <1/100)

Rare (>1/10,000, <1/1,000)

Very rare (<1/10,000), including isolated reports

Unknown (cannot be estimated from the data available).

MedDRA system organ class -Frequency

- Gastrointestinal disorders including dyspepsia, anorexia, nausea, diarrhoea or constipation - Unknown
- Allergic skin reactions : rash, urticaria, pruritis - Unknown
- Fatigue and restlessness - Unknown

Other adverse reactions that have been reported include headaches, neuropathy, anxiety, dizziness and mania

Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight or strong ultra-violet (UV) irradiation.

If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Signs and symptoms

After the intake of up to 4.5 g dry extract per day for 2 weeks and additionally 15 g dry extract just before hospitalisation seizures and confusion have been reported.

Management of Overdose

When a large overdose has occurred, phototoxic reactions may occur. The skin of the patient should be protected for 1-2 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants ATC code: N06AX

Hypericum dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonin and dopamine. Subchronic treatment causes a down-regulation of β -adrenergic receptors; it changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) similarly to synthetic antidepressants. Naphodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity.

5.2 Pharmacokinetic properties

The absorption of hypericin is delayed and starts about 2 hours after administration. The elimination half-life of hypericin is about 20 hours, the mean residence time about 30 hours. Maximum hyperforin levels are reached about 3-4 hours after administration; no accumulation could be detected. Hyperforin and the flavonoid miquelianin can cross the blood-brain-barrier. Hyperforin induces the activity of the metabolic enzymes CYP3A4, CYP2C9, CYP2C19 and PGP dose-dependently via activation of the PXR system. Therefore the elimination of other drug substances may be accelerated, resulting in decreased plasma concentrations.

5.3 Preclinical safety data

Studies on acute toxicity and repeated dose toxicity did not show signs of toxic effects. The weak positive results of an ethanolic extract in the AMES-test (Salmonella typhimurium TA 98 and TA 100, with and without metabolic activation) could be assigned to quercetin and are irrelevant to human safety.

No signs of mutagenicity could be detected in further in-vitro and in-vivo test systems. Tests on reproductive toxicity revealed equivocal results with some data suggesting that hypericin may have teratogenic effects. Tests on the carcinogenic potential have not been published.

Phototoxicity: After oral application of dosages of 1800 mg of an extract per day for 15 days the skin sensitivity against UVA was increased, and the minimum dose for pigmentation was significantly reduced. In the recommended dosage, no signs of phototoxicity are reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maltodextrin
Colloidal anhydrous silica
Microcrystalline cellulose
Croscarmellose sodium
Sodium starch glycolate (type A)
Magnesium stearate

Tablet Coating:

Hypromellose
Sucrose
Talc
Calcium carbonate (E170)
Tragacanth
Acacia
Liquid glucose
Titanium dioxide (E171)
Iron oxide hydrate (E172) (yellow iron oxide)
Vanillin
White beeswax
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.

6.5 Nature and contents of container

Binary blisters made of PVC / PVDC and aluminium.
Packs of 30, 60, 90 or 100 coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1457/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th February 2015

10 DATE OF REVISION OF THE TEXT

April 2016