SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CAFFETIN LADY® 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen (in a form of ibuprofen lysinate).

Excipients with known effect:
Each film-coated tablet contains glucose, colour Sunset yellow FCF aluminium lake (E110), colour Ponceau 4R aluminium lake (E124) and soya lecithin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Film-coated tablets

Pastel-pink with shiny effect, oblong, biconvex film-coated tablets with break mark on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of dysmenorrhoea.

4.2 Posology and method of administration

For oral administration and short-term use only.
During the short-term use, if symptoms persist or worsen the patient should be advised to consult a doctor.

The lowest effective dose should be used for the shortest duration necessary to relieve the symptoms (see section 4.4).

Adults and children and adolescents between 12 and 18 years:
Children and adolescents between 12 and 18 years: Take 1 or 2 tablets with water, up to three times a day as required.
Adults: Take 1 or 2 tablets with water, up to three times a day as required.

Leave at least four hours between doses.
Do not take more than 6 tablets in any 24 hour period.

Not for use by children under 12 years of age.

Patients with gastric disorders should take the tablets with food.

Drug intake should not continue for more than 3 days without doctor's advice.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Severe heart failure (NYHA Class IV), renal failure or hepatic failure (see section 4.4).
- Conditions involving an increased tendency to bleeding;
- Last trimester of pregnancy;
- Hypersensitivity to peanut or soya.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory
Bronchospasm may be precipitated in patients suffering from, or with a previous history of, bronchial asthma or allergic disease.

Other NSAIDs
The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease
Systemic lupus erythematosus as well as those with mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8)

Renal
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8). There is

a risk of renal impairment in dehydrated children and adolescents.

Hepatic
Hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.
Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200 mg/day) is associated with an increased risk of arterial thrombotic events.
Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.
Careful consideration should also be exercised before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility
There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Gastrointestinal
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).
GI bleeding, ulceration or perforation, which can be fatal has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.
Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Severe skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use

of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections
This medicinal product can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When this medicine is administered for pain or fever in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

The film-coated tablets contain the colours E110 and E124, which may cause allergic reactions.
This product contains soya lecithin. Patients allergic to peanut or soya, should not use this medicinal product.
This product contains glucose. Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be avoided in combination with:

Aspirin (Acetylsalicylic Acid): Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects unless low-dose aspirin (not above 75 mg daily) has been advised by a doctor (see Section 4.4). Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ibuprofen should be used with caution in combination with:

Corticosteroids: as these may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4).

Antihypertensives and diuretics: since NSAIDs may diminish the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or

angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

Ant-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: There is evidence for potential increase in plasma levels of lithium.

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

4.6 Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryofoetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, Caffetin Lady should not be given unless

clearly necessary. If Caffetin Lady is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;

the mother and the neonate, at the end of the pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Caffetin Lady is contraindicated during the third trimester of pregnancy.

Lactation/Breastfeeding
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility
See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The list of the following adverse events relates to those experienced with ibuprofen at OTC doses for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

Clinical studies suggest that use of ibuprofen, particularly at a high dose 2400 mg/day may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic	Very rare	Haematopoietic disorders (anaemia,

System Disorders		leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune System Disorders		Hypersensitivity reactions consisting of[1]:
	Uncommon	Urticaria and pruritus
	Very rare	Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).
	Not known	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[2]
Cardiac Disorders	Not known	Cardiac failure and oedema
Vascular Disorders	Not known	Hypertension
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea, dyspepsia
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.
	Not known	Exacerbation of colitis and Crohn's disease (section 4.4).
Hepatobiliary Disorders	Very rare	Liver disorders
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes
	Very rare	Severe forms of skin reactions such as bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary Disorders	Very rare	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.
	Not known	Renal insufficiency
Investigations	Very rare	Decreased haemoglobin levels

Description of Selected Adverse Reactions

[1] Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

[2] The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

4.9 Overdose

In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms:

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management:

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids.
ATC code: M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose

aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin (acetylsalicylic acid) dosing (81mg), a decreased effect of (acetylsalicylic acid) on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is rapidly absorbed following oral administration, especially in a form of ibuprofen lysinate. Peak plasma concentrations are reached 0.5 hours after ingestion. Absorption is more rapid when ibuprofen is given under fasting conditions.

Distribution
Ibuprofen is rapidly distributed throughout the whole body and like most drugs of its class is highly protein bound (90-99%).

Metabolism
Ibuprofen metabolism is fast. 90% of the ingested dose is metabolized in a form of inactive metabolites.

Elimination
Ibuprofen is eliminated in the urine. The excretion of ibuprofen is more than 90% for 24 hours after the last dose, mainly in a form of metabolites or their conjugates, and only 10% unchanged. Due to the fast metabolism, ibuprofen does not cumulate, even after prolonged administration.
Half-life of plasma elimination is approximately 2.0 hours and does not change significantly when the dose increases.

5.3 Preclinical safety data

There are no preclinical data of relevance, which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Silicified microcrystalline cellulose (Cellulose, microcrystalline and Silica, colloidal anhydrous);
Copovidone;
Croscarmellose sodium;

Silica, colloidal anhydrous;
Magnesium stearate;
Talc

Film coating
Opadry II pink (hypromellose; titanium dioxide (E171); polydextrose; talc; maltodextrin; medium chain triglycerides; ponceau 4R aluminium lake (E124); FD&C Yellow #6/Sunset yellow FCF aluminium lake (E110); FD&C Blue #2/Indigo carmine aluminium lake (E132));
Opadry fx silver (carmellose sodium; maltodextrin; glucose monohydrate; mica-based pearlescent pigment (mica (E555)/titanium dioxide (E171)); lecithin (soya)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

Three (3) years.

6.4 Special precautions for storage

Store at temperature below 25 ˚C.

6.5 Nature and contents of container

CAFFETIN LADY® film-coated tablets are immediate packed in press-through blisters (Al foil/PVC foil), perforated for individual doses, each blister containing 10 tablets.
The cardboard box contains 10 tablets (1 blister) and a leaflet inside.

6.6 Instructions for use/handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER AND MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT