Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tefin 150 mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 150 mg of ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository.
White, odourless, torpedo-shaped suppository.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of mild to moderate pain and fever in children of 3 years or older and with body weight of at least 15kg.

4.2 Posology and method of administration

Posology:

Paediatric population

Details on the posology are available in the following tables. The dosage of Tefin for children and young persons depends on the patient's age and body weight. In general, the single dose is 7 to 10 milligrams per kilogram body weight and the maximum daily dose 30 milligrams per kilogram body weight.
The dosage interval depends on the symptoms and the maximum daily dose and should be at least six hours.

If Tefin is required for 3 days or if symptoms worsen, a doctor should be consulted.

Age	Body weight	Single dose	Maximum daily dose
3 to 6 years	15 to 20 kilogram	1 Suppository (150 milligram)	3 Suppositories (450 milligram daily)
6 to 9 years	20 to 29 kilogram	1 Suppository (150 milligram)	4 Suppositories (600 milligram daily)

Method of administration and duration of treatment:

Tefin suppositories should be put deep into the rectum after bowel movement. They may be warmed up in the hands or dipped for a short time into warm water to improve their sliding properties.

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

Special populations

Elderly patients:
No adjustment of dosage is required. Due to possible side-effects (see section 4.4), elderly people should be carefully monitored.

Impaired renal function:
No reduction of dosage is required in patients with slightly to moderately impaired renal function (patients with severe renal insufficiency: see section 4.3.).

Impaired liver function:
No reduction of dosage is required in patients with slightly to moderately impaired liver function (patients with severe liver disorder: see section 4.3.).

Children and adolescents:
Due to the dosage of their active substance, Tefin 150 milligram suppositories are not suited for the treatment of children with a body weight below 15 kilograms (3 years).

4.3 Contraindications

Tefin is contraindicated in the presence of the following disorders:

- hypersensitivity to ibuprofen or to any of the excipients,
- known reactions like bronchospasm, angioedema, asthma, rhinitis or urticaria to the ingestion of acetylsalicylic acid or any other NSAIDs in the past,
- residual disorders of the blood count,
- active gastric or duodenal ulcer or haemorrhage with at least two clearly identified episodes of proven ulceration or bleeding or history of such disorders,
- history of gastrointestinal bleeding or perforation due to treatment with NSAIDs,
- cerebrovascular or other active bleeding,
- severe impairment of liver or kidney function,
- severe heart failure (NYHA Class IV)
- in the last three months of pregnancy (see section 4.6).

Due to the dosage of their active substance, Tefin 150 milligram suppositories are not suitable for the treatment of children with a body weight below 15 kilograms (3 years).

4.4 Special warnings and precautions for use

Gastrointestinal safety
The concomitant use of Tefin and other NSAIDs including selective Cox-2 inhibitors should be avoided.

The intensity of adverse reactions can be diminished by giving the smallest effective amount over the shortest possible period (see section 4.2 and gastrointestinal and cardiovascular risks in the following text).

Elderly patients:
Undesirable effects, especially gastrointestinal bleeding and perforation, including fatalities, occur with greater frequency in elderly patients on NSAIDs (see section 4.2).

Gastrointestinal bleeding, ulcers and perforation:
Gastrointestinal bleeding, ulcers or perforation, even with fatal outcome, have been reported in connection with all NSAIDs. These reactions occurred with or without previous warning symptoms at any time during treatment and in patients with or without a history of severe gastrointestinal events.

In patients with a history of gastric or duodenal ulcers and in elderly subjects, the risk of gastrointestinal bleeding, ulceration and perforation rises with increasing doses of NSAIDs, especially if these ulcers were associated with bleeding and perforation (see section 4.3 "Contraindications"). In such cases, treatment should be started with the smallest dose. Combination of NSAIDs with medicinal products protecting the gastrointestinal tract (e.g. misoprostol or proton pump inhibitors) should be considered. This applies also to patients needing low-dose acetylsalicylic acid or other active substances which increase the risk of gastrointestinal side-effects (see below and section 4.5).

Patients who have been affected with gastrointestinal disorders, especially elderly people, should report any unusual gastrointestinal symptoms (especially gastrointestinal bleeding), particularly at the start of therapy.

Caution must be exercised in patients who concomitantly receive medicinal products which might increase the risk of gastric toxicity or bleeding, such as oral corticoids, anticoagulants like warfarin, selective serotonin uptake inhibitors or platelet aggregation inhibitors like acetylsalicylic acid (see section 4.5).

Treatment with Tefin must be discontinued when the patient develops gastrointestinal bleeding and ulcers.

NSAIDs should be used with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), because their condition may get worse (see section 4.8).

Cardiovascular and cerebrovascular effects:

Caution must be exercised in patients having a history of high blood pressure and/or myocardial insufficiency (heart failure), since fluid retention, hypertension and oedema have been reported in connection with the use of NSAIDs (the physician or pharmacist should be consulted before start 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). 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 long-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.

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 NSAIDSs (see section 4.8). Patients appear to be at highest risk of 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:
Tefin 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 Tefin is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Tefin suppositories in case of varicella.

Other notes:

Tefin should only be used after balancing of risks and benefits in case of
- congenital disturbance of porphyrin metabolism (e. g. acute intermittent porphyria),
- systemic lupus erythematosus (SLE) and mixed collagen disease (mixed connective tissue disease) (see section 4.8).

Close medical supervision is necessary in the presence of
- gastrointestinal disorders or chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease),
- hypertension or cardiac failure,
- impaired renal function,
- hepatic dysfunction,
- immediately after major surgery,
- in patients with hay fever, nasal polyps or chronic obstructive airways disease, since these patients are at greater risk of allergic reactions, which may be manifested as asthmatic attacks (analgesic asthma), Quincke's oedema or urticaria,

- in patients developing allergic reactions to other drugs, because they are at a greater risk of hypersensitivity reactions to Tefin suppositories.

Severe acute hypersensitivity reactions such as anaphylactic shock have very rarely been seen. Treatment with Tefin should be stopped when the patient shows the first signs of hypersensitivity reactions. Professional assistance should be sought immediately to institute appropriate measures to eliminate these symptoms.

Ibuprofen, the active substance of Tefin, may cause a temporary inhibition of blood platelet function (platelet aggregation). Patients with coagulation disorders (e.g. idiopathic thrombocytopaenic purpura (ITP), intracranial haemorrhage or bleeding diathesis) should therefore be carefully monitored.

There is a risk of renal impairment in dehydrated children. Caution is required in patients with renal impairment (see section 4.3) since renal function may deteriorate. The habitual use of analgesics, especially of active substance mixtures, may lead to permanent kidney damage including the risk of kidney failure (analgesic nephropathy).

Caution is required in patients with hepatic impairment (see section 4.3 and 4.8)

In case of long-term treatment with Tefin, liver and kidney function should be monitored and blood counts should be carried out on a regular basis.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Improper use of large amounts of analgesics for extended periods of time may cause headache, which must not be treated with increased doses of the medicinal product concerned.

Alcoholic beverages in combination with NSAIDs may increase the side-effects caused by their active substance, especially reactions affecting the gastrointestinal tract and the central nervous system.

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment see section 4.6

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

Caution is required in patients with disorders of the anus or lower rectum.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (as with other NSAIDs) should be given with great caution in combination with the following active substances:

Acetylsalicylic acid
Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose 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:
Owing to synergistic effects, the concomitant use of several NSAIDs including selective Cox-2 inhibitors may increase the risk of gastrointestinal ulcers and bleeding. Ibuprofen should therefore not be given in combination with other NSAIDs (see section 4.4).

Digoxin, phenytoin, lithium:
The concomitant use of Tefin with digoxin, phenytoin or lithium medications can increase the plasma level of these drugs. As a rule the plasma-lithium-level, plasma-digoxin- and plasma-phenytoin-level need not to be controlled, if ibuprofen is used properly (not more than 3 days).

Diuretics, ACE inhibitors, adrenergic beta-antagonists and angiotensin-II inhibitors:
NSAIDs may reduce the effects of diuretics and antihypertensives. In patients with impaired renal function (e. g. dehydrated or elderly patients), the concomitant use of ACE inhibitors, adrenergic beta-antagonists or angiotensin-II inhibitors with drugs inhibiting cyclooxygenase may cause renal function to get worse and acute renal failure may ensue. This reaction is usually reversible. Such drug combinations should therefore be used with caution, especially in the elderly patients. Patients should be adequately hydrated before treatment with Tefin is initiated and adequate hydration maintained during treatment. Regular renal function tests after the start of treatment should be considered. The concurrent use of Tefin and potassium-sparing diuretics may lead to hyperkalaemia.

Glucocorticoids:
Increased risk of gastrointestinal ulcers and bleeding (see section 4.4).

Platelet aggregation inhibitors like acetylsalicylic acid, dipyridamole, clopidogrel and selective serotonin uptake inhibitors:
Increased risk of gastrointestinal bleeding (see section 4.4)

Methotrexate:
The treatment of Tefin within 24 hours before or after the use of methotrexate may increase the concentration of methotrexate and its toxic action.

Ciclosporin:
The risk of damage to the kidneys by ciclosporin is increased by the concomitant use of NSAIDs. This effect cannot be ruled out for combinations of ciclosporin with ibuprofen.

Anticoagulant agents:
NSAIDs may increase the action of anticoagulants like warfarin and heparin (see section 4.4). It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Sulphonylureas:
Clinical studies have revealed that NSAIDs interact with oral antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been reported, monitoring blood glucose levels is advised in patients receiving these drugs concomitantly.

Tacrolimus:
Concurrent use of tacrolimus and ibuprofen increases the risk of renal toxicity.

Zidovudine:
There is some evidence to suggest that this active substance increases the risk of haemarthrosis or haematoma in HIV- positive haemophiliacs, who concomitantly receive zidovudine and ibuprofen.

Probenicid and sulphinpyrazone:
Products containing probenecid or sulphinpyrazone may delay the metabolism and excretion of ibuprofen.

Aminoglycosides: Reduction in renal function may occur in susceptible individuals with decreased elimination of aminoglycoside and increased plasma concentrations.

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

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 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal 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 embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, Tefin use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Tefin should not be given unless clearly necessary. If Tefin 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Tefin for several days from gestational week 20 onward. Tefin should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of 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, Tefin is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

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

Fertility

There is some evidence that active substances which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

As Tefin suppositories given in high doses may cause central nervous system-related side-effects such as fatigue and dizziness, the patient's reaction can be modified and his ability to drive a car or operate machinery can be impaired.This is especially true when alcoholic beverages are taken simultaneously.

4.8 Undesirable effects

Undesirable effects are presented according to the following incidence:
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 (Incidence cannot be estimated from the available data)

The following list of undesirable effects contains all known side-effects observed during treatment with ibuprofen, including those reported by patients suffering from rheumatism and undergoing long-term therapy with large doses of this drug. Incidence rates exceeding very rare reports relate to short-term treatment with daily doses of up to 1,200 milligrams of orally given ibuprofen and not more than 1,800 milligrams administered in the form of suppositories (12 suppositories of Tefin 150 milligrams).

As regards the following undesirable effects, it should be kept in mind that most of them are dose-related and vary considerably among individuals.

The most common side-effects affect the gastrointestinal tract. Peptic ulcer, perforation or bleeding (including fatalities) may occur, especially in the elderly (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, digestive complaints, abdominal pain, melaena, haematemesis, ulcerative stomatitis, aggravation of colitis and Crohn's disease (see section 4.4) have been reported in connection with the use of ibuprofen. Gastritis was observed less frequently. In particular, the risk of bleeding from the gastrointestinal tract depends on the dose range and the duration of treatment.

Oedema, hypertension and heart failure were reported in connection with the use of NSAIDs.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) and in long-term treatment 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**
Cardiac disorders	Very rare	Palpitation, heart failure, heart attack
Blood and lymphatic system disorders	Very rare	Haemopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first signs may be: fever, sore throat, superficial ulcers in the mouth, flu symptoms, lassitude, nasal bleeding and ecchymosis (see note 1 below).
Nervous system disorders	Uncommon	Nervous system disorders like headache, dizziness, insomnia, agitation, irritability or fatigue.
Eye disorders	Uncommon	Vision disorders.
Ear and labyrinth disorders	Rare	Tinnitus.
Gastrointestinal disorders	Common	Heartburn, abdominal pain, dyspepsia, nausea, diarrhoea, flatulence, constipation and vomiting, minor blood loss from the gastrointestinal tract, giving rise to anaemia in exceptional cases. The administration of suppositories may cause local irritation, secretion of bloody mucus or painful defaecation.
	Uncommon	Gastrointestinal ulceration, sometimes accompanied by gastrointestinal bleeding (haematemesis, melaena and haematemesis) and perforation (gastrointestinal bleeding is sometimes fatal, especially in the elderly) (see note 2 below). Gastritis. Ulcerative stomatitis, aggravation of ulcerative colitis and Crohn's disease (see section 4.4).
	Very rare	Oesophagitis, pancreatitis.
Renal and urinary disorders	Very rare	Development of oedema, especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis, which can be accompanied by acute renal insufficiency. Damage to the renal tissue (papillary necrosis) and elevated uric acid concentrations in the blood are very rarely encountered. Decreased urea excretion can occur (see note 3 below).
Skin and subcutaneous tissue disorders	Very rare	Erythema multiforme, purpura. Bullous and exfoliative skin reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis. In exceptional cases, varicella infection may be

		accompanied by severe skin infections and complications affecting the soft tissues (see "Infections and infestations").
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions.
Infections and infestations	Very rare	Aggravation of infections (e.g. development of a necrotising fasciitis) having a temporal association with the systemic administration of non-steroidal anti-inflammatory drugs has been reported. This reaction maybe related to the mode of the action on non-steroidal anti-inflammatory drugs (see note 4 below). During treatment with ibuprofen, symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or disorientation have been observed. Patients with a disease of the immune system (systemic lupus erythematosus, mixed connective tissue disease) seem to be predisposed.
Vascular disorders	Very rare	Arterial hypertension.
Immune system disorders	Uncommon	Hypersensitivity reactions with rash, urticaria, itching and asthmatic attacks (possibly with fall in blood pressure) (see note 5 below).
	Very rare	Severe hypersensitivity reactions. These can be manifested as facial oedema, swelling of the tongue, larynx with constriction of the airways, tachycardia, fall in blood pressure including life-threatening shock (anaphylaxis, angioedema or severe shock) (see note 6 below).
Hepatobiliary disorders	Very rare	Impaired liver function, liver damage, especially in patients on long-term treatment, hepatic failure, acute hepatitis, cholestatic jaundice, elevation of liver enzymes.
Psychiatric disorders	Very rare:	Psychotic reactions, depression.
Respiratory, thoracic and mediastinal disorders	Very rare	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Investigations	Very rare	Haemoglobin decreased, urea renal clearance decreased.

Notes (see reference numbers in the above table):

1. During long-term treatment, blood count should be monitored regularly.
2. Patients should be advised to stop treatment and immediately consult the doctor if severe epigastric pain, gastrointestinal bleeding, melaena or haematemesis occur.
3. Renal function should be monitored on a regular basis especially during long term treatment.
4. Patients should be advised to immediately consult a physician, whenever infections occur or get worse during the treatment with Tefin. In such cases, the use of anti-infectives/antibiotics should be considered.
5. If symptoms of hypersensitivity occur, the patient should be advised to discontinue treatment with Tefin and consult the doctor immediately.
6. Symptoms of severe hypersensitivity may occur even after the first dose. If these symptoms occur, the patient should be advised to contact emergency services immediately.

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 the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

A dose in excess of 200mg/kg carries a risk of causing toxicity.

a) Symptoms of overdosing:
Overdosing may lead to CNS-related disorders like headache, dizziness, somnolence and unconsciousness (in children also myoclonic spasms) and abdominal pain, diarrhoea, nausea and vomiting. Tinnitus, headache, nystagmus, blurred vision, hypotension and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as dizziness, drowsiness, loss of consciousness, 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.

b) Therapeutic measures in case of overdose:

There is no specific antidote. Patients should be treated symptomatically as required. Use supportive care where appropriate. Management should include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. 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: nonsteroidal anti-inflammatory and analgesic drugs. ATC Code: M01AE01.

Ibuprofen is a nonsteroidal anti-inflammatory and analgesic active substance. In the commonly used animal models, its effect was shown to be due to the inhibition of prostaglandin synthesis. In humans, the active substance alleviates pain, swelling and fever caused by inflammation. Furthermore, ibuprofen inhibits theADP and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), 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

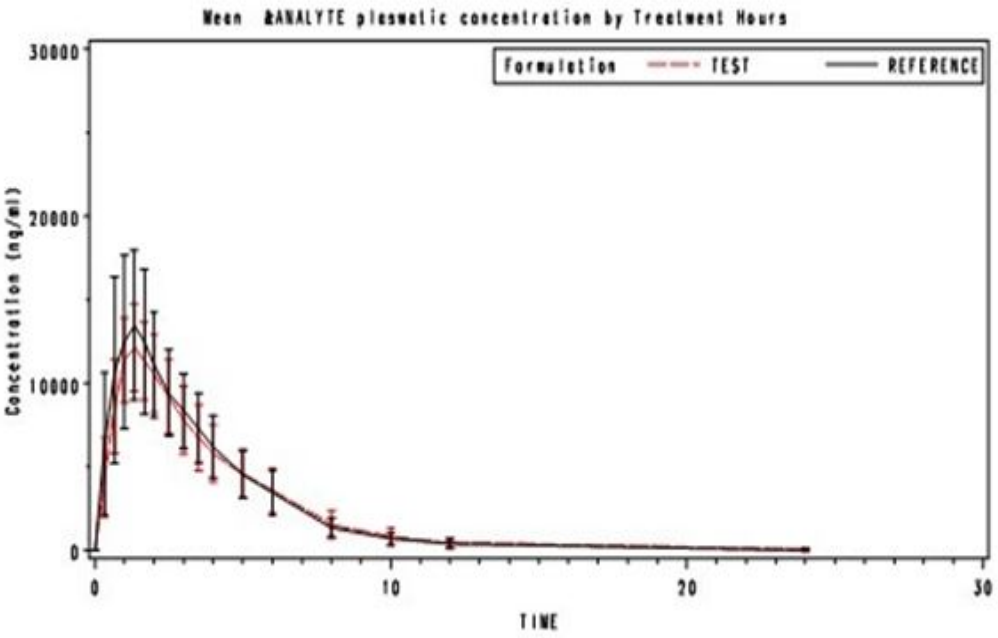
Orally given ibuprofen is partly absorbed in the stomach and completely absorbed from the small intestine. Following rectal administration, the active substance is almost completely absorbed, reaching plasma concentrations similar to those seen after oral ingestion. Peak plasma levels occur in one to two hours after oral administration. Ibuprofen is bound to plasma proteins to the extent of 99 per cent.

After metabolization in the liver (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely excreted, mainly through the kidneys (90 per cent) and partly in the bile. The elimination half-life is about two hours.

The following results were achieved in a bioavailability study performed in 2004 in 28 healthy volunteers, in comparison with a reference standard:

	Test preparation Tefin 150 milligram suppositories (ibuprofen)	**Reference standard Ibuprofen suspension 150 milligram (oral)**
Peak plasma concentration (Cmax, µg/ml):	**12.8 ± 2.6**	**16.6 ± 3.1**

Time of peak plasma concentration (tmax, hr): Area under the plasma concentration-time curve (AUC, µg/ml*hr):	**1.443 ± 0.455**	**1.285 ± 0.635**
	53.94 ± 14.85	**56.25 ± 12.68**
These values are expressed (AUC$_{0-inf}$) *is 95.50 % in relation to the oral suspension (reference standard)*		
Average course of plasma concentrations in comparison with a reference standard in a concentration-time diagram:		



5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments showed up mainly in form of lesions and ulcerations in the gastro-intestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.
Ibuprofen inhibited ovulation in rabbits and impaired implantation in different animal species (rabbit, rat, and mouse). Reproductive toxicity studies conducted in rats and rabbits have demonstrated that ibuprofen passes the placenta; for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Blister strips of aluminium/polyethylene containing five suppositories.

Pack sizes of 10 suppositories and hospital-only 100 pack sizes (10 x 10)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
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8 MARKETING AUTHORISATION NUMBER

PA0126/330/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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