Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nuprin 75mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 75mg acetylsalicylic acid (aspirin).

Excipient with known effect:
Each gastro-resistant tablet contains 0.0016 mg sodium (Essentially 'sodium-free').

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

75 mg: Yellow to light yellow, oval, biconvex gastro-resistant tablets, 9.2 x 5.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Secondary prevention of myocardial infarction.
- Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
- History of unstable angina pectoris, except during the acute phase.
- Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
- Coronary angioplasty, except during the acute phase.
- Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.

Nuprin is not recommended in emergency situations. It is restricted to secondary prevention with chronic treatment.

4.2 Posology and method of administration

Adults
Secondary prevention of myocardial infarction:
The recommended dose is 75-160 mg once daily.

Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris:
The recommended dose is 75-160 mg once daily.

History of unstable angina pectoris, except during the acute phase:
The recommended dose is 75-160 mg once daily.

Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG):
The recommended dose is 75-160 mg once daily.

Coronary angioplasty, except during the acute phase:
The recommended dose is 75-160 mg once daily.

Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out:
The recommended dose is 75-325 mg once daily.

Elderly
In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency (see sections 4.3 and 4.4). Treatment should be reviewed at regular intervals.

Paediatric population
Acetylsalicylic acid should not be administered to children and adolescents younger than 16 years, except on medical advice where the benefit outweighs the risk (see section 4.4).

Method of administration
For oral use.

The tablets should be swallowed whole with sufficient fluid (1/2 glass of water). Due to the gastro resistant coating the tablets should not be crushed, broken or chewed because coating prevents irritant effects on the gut.

4.3 Contraindications

- Hypersensitivity to aspirin (e.g. bronchospasm, rhinitis, urticaria), to non-steroidal anti-inflammatory drugs or to any of the excipients listed in section 6.1;
- Hypoprothrombinaemia, haemophilia, haemorrhagic disease or a history of bleeding disorders, cerebral haemorrhage and active peptic ulceration.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic impairment;
- Severe renal impairment;
- Severe heart failure
- Doses >100 mg/day during the third trimester of pregnancy (see section 4.6);
- Methotrexate used at doses >15mg/week (see section 4.5).

4.4 Special warnings and precautions for use

Nuprin is not suitable for use as an anti-inflammatory/analgesic/antipyretic.

Undesirable effects associated with non-steroidal anti-inflammatory drugs (NSAIDs) may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Recommended for use in adults and adolescents from 16 years of age. There is a possible association between aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children and adolescents aged under 16 years unless specifically indicated.

The use of Nuprin with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. Where prolonged therapy is required, patients should be reviewed regularly.

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. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5)

Patients with a history of GI toxicity, particularly when 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 or selective serotonin-reuptake inhibitors, or anti-platelet agents such as clopidogrel and dipyridamole (see section 4.5)

When GI bleeding or ulceration occurs in patients receiving Nuprin, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8 undesirable effects).

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Acetylsalicylic acid is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin should be used with caution in patients with a history of peptic ulceration, inflammatory bowel disease or coagulation abnormalities. These may also induce gastro-intestinal haemorrhage, occasionally major.

Acetylsalicylic acid should be used with caution in patients with moderately impaired renal, cardiac or hepatic function (avoid if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including aspirin especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

In patients with strokes, aspirin should not be given until the possibility of cerebral haemorrhage has been excluded.

Acetylsalicylic acid may also precipitate bronchospasm or induce asthma attacks or other hypersensitivity reactions in susceptible subjects. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

High doses of aspirin may precipitate acute haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.

Aspirin decreases platelet adhesiveness and increases bleeding time. Haematological and haemorrhagic effects can occur, and may be severe. Patients should report any unusual bleeding symptoms to their physician.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven-Johnsons syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (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. Acetylsalicylic acid should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Concomitant treatment with Acetylsalicylic acid and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, fibrinolytics, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Acetylsalicylic acid can reduce uric acid excretion. and should be used with care in patients with gout or a history of gout.

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Care should be taken when stopping in those patients with multiple risk factors as the risk of a cerebrovascular event in the four weeks after aspirin discontinuation is significant. The risk/benefit of stopping aspirin therapy in the case of patients undergoing surgery should be considered.

Excipient Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations
Methotrexate (used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses > 15 mg/week) with Nuprin is contraindicated (see section 4.3).

Not recommended combinations
Uricosuric agents, e.g. probenecid
Salicylates reverse the effect of probenecid. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account
Anticoagulants e.g. coumarin, heparin, warfarin
Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision. The bleeding time should be monitored (see section 4.4).

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)
Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulphonylureas
Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.
Diuretics: Risk of acute renal failure due to the decreased glomerual filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

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

Carbonic anhydrase inhibitors (acetazolamide)
Concurrent administration of carbonic anhydrase inhibitors, such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Systemic corticosteroids
Plasma salicylate concentrations may be reduced by concurrent use of corticosteroids, and salicylate toxicity may occur following withdrawal of the corticosteroids. The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Methotrexate (used at doses <15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs
Avoid concomitant use with other NSAIDs. Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Metamizole
Metamizole may reduce the effect of acetylsalicylic acid (aspirin) on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardio protection.

Cyclosporin, tacrolimus
Concomitant use of NSAIDs and cyclospoin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Gold
Risk of increased hepatotoxicity with aspirin.

Aminoglycosides
Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations

Thiopental
Aspirin may potentiate the effects of thiopental anaesthesia

Oral hypoglycemic agents
Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Antacids
Patients using gastro-resistant aspirin should be advised against ingesting antacids simultaneously, to avoid premature drug release.

Valproate
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol
Concomitant administration of alcohol and acetylsalicylic acid may increase the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Fertility
Women attempting to conceive should not use any NSAID, including aspirin, because of the findings in a variety of animal models that indicate these agents block blastocyst implantation.

Pregnancy
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

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 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. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid 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 oligo-hydroamniosis;

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, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation:
As aspirin is secreted into breast milk, Nuprin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

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 with Nuprin.

Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, no influence on the reactivity and the ability to drive or use machines is expected.

4.8 Undesirable effects

Summary of the safety profile
The most commonly observed adverse events are gastrointestinal in nature.

Tabulated list of adverse reactions
Undesirable effects are listed by MedDRA System Organ Classes. Assessment of undesirable effects is based on the following frequency groupings:

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)

System Organ Class	*Undesirable Effect*
Blood and lymphatic system disorders	*Common:* Increased bleeding tendencies. *Rare:* Thrombocytopenia, granulocytosis, aplastic anaemia. *Not known:*

	Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).
Immune system disorders	*Rare:* Hypersensitivity reactions including skin rashes, urticaria, angi-oedema, asthma, bronchospasm, allergic oedema and anaphylactic reactions including shock. *Not known:* Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome
Metabolism and digestive system disorders	*Not known:* Hyperuricaemia.
Nervous system disorders	*Rare:* Intracranial haemorrhage *Not known:* Headache, vertigo, cerebral haemorrhage.
Ear and labyrinth disorders	*Not known:* Reduced hearing ability; tinnitus.
Cardiac disorders	*Not known:* Cardiac failure
Vascular disorders	*Rare:* Haemorrhagic vasculitis. *Not Known:* Hypertension, Haemorrhages[1], Haematoma[1]
Respiratory, thoracic and mediastinal disorders	*Uncommon:* Rhinitis, dyspnoea. *Rare:* Bronchospasm, asthma attacks. *Not Known:* Epistaxis Haemoptysis
Reproductive system and mammary disorders	*Rare:* Menorrhagia
Gastrointestinal disorders[2]	*Common:* Dyspepsia. *Rare:* Severe gastrointestinal haemorrhage, nausea, vomiting. *Not known:* Gastric, gastrointestinal or duodenal ulcers and perforation[3]. GI Bleeding[3] Nausea Vomiting Diarrhoea Flatulence

	Constipation Dyspepsia Abdominal pain Melaena Haematemesis Ulcerative stomatitis Exacerbation of colitis Exacerbation of Crohn's disease Gastritis
Hepatobiliary disorders	*Not known:* Hepatic insufficiency.
Skin and subcutaneous tissue disorders	*Uncommon:* Urticaria. *Rare:* Steven-Johnsons syndrome, Lyell's syndrome, purpura, erythema nodosum, erythema multiforme. *Not Known:* Ecchymoses
Renal and urinary tract disorders	*Not known:* Impaired renal function Haematuria Urate kidney stones.
General disorders and administration site disorders	*Not known:* Oedema
Investigations	*Not known* Bleeding time prolonged

[1]May occur in various organ systems and may be fatal
[2]The special coating of Nuprin helps to reduce the incidence of side effects resulting from gastric irritation.
[3]Sometimes fatal, particularly in the elderly

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
Website: www.hpra.ie

4.9 Overdose

Salicylate toxicity (> 100 mg/kg/day over 2 days may produce toxicity) may result from chronic, therapeutically acquired, intoxication, and from, potentially life-threatening, acute intoxications (overdose), ranging from accidental ingestions in children to incidental intoxications.

If overdosage is suspected, the patient should be kept under observation for at least 24 hours, as symptoms and salicylate blood levels may not become apparent for several hours. With the gastro-resistant formulation, peak plasma levels may not occur for up to 12 hours.

Chronic salicylate poisoning can be insidious as signs and symptoms are non-specific. Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses.

Symptoms
Common features include dizziness, vomiting, nausea, dehydration, tinnitus, vertigo, deafness, sweating, headache, confusion, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Symptoms may be controlled by reducing the dosage. Tinnitus can occur at plasma concentrations of 150 to 300 micrograms/mL. More serious adverse events occur at concentrations above 300 micrograms/mL.

The principal feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. The most common presentation for a child is metabolic acidosis. The severity of poisoning cannot be estimated from plasma concentration alone. Absorption of acetylsalicylic acid can be delayed due to reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. Management of acetylsalicylic acid intoxication is determined by its extent, stage and clinical symptoms and according standard poisoning management techniques. Predominant measures should be the accelerated excretion of the drug as well as the restoration of the electrolyte and acid-base metabolism.

Uncommon features include tachypnoea, diaphoresis, haematemesis, hyperpyrexia, hypoglycaemia, hyperglycaemia, increased ketone levels, hypokalaemia, hypernatraemia, hypoprothrombinaaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, dehydration, oliguria, renal failure, GI bleeding non-cardiogenic pulmonary oedema, asphyxiation, respiratory arrest, dysarrhythmias, hypotension, and cardiovascular arrest.

Central nervous system features including confusion, disorientation, lethargy, coma, convulsions and toxic encephalopathy are less common in adults than in children.

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Management
Gastric lavage or repeated administration of activated charcoal if an adult present within one hour of ingestion of more than 125 mg/kg. The plasma salicylate concentration should be measured for patients who have ingested >125mg/kg. However, the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Urea and electrolytes, INR/PTR, blood pressure, ECG alteration and blood glucose should be monitored. Elimination is increased by urinary alkalisation, which is achieved by the administration of intravenous sodium bicarbonate. The urine pH should be monitored, and further intravenous sodium bicarbonate may be required to maintain urinary pH 7.5-8.5 (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years and over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin, ATC code: B01A C06.

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions.
Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%.
Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.
Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.
In one study, when a single dose of ibuprofen 400 mg was 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. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Absorption
After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption.

After intake of Nuprin gastro-resistant tablets the maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after about 5 hours and 6 hours, respectively, following administration in the fasted state. If the tablets are taken with food, maximum plasma levels are reached approximately 3 hours later than in the fasted state.

Distribution
Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight. Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Biotransformation
Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates, and traces of gentisic acid.
Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses, 12 hours after usual analgetic doses and 15-30 hours after high therapeutic doses or intoxication.
Elimination
Salicylic acid and its metabolites are predominantly excreted via the kidneys.

5.3 Preclinical safety data

The nonclinical safety profile of acetylsalicylic acid is well documented.

In experimental animal studies, salicylates have shown no other organ injury than renal damage.

In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications.

Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Maize starch
Silica, colloidal anhydrous
Stearic acid

Seal coat:
Opadry clear YS-1-7006 containing-

Hypromellose
Polyethylene glycol (Macrogol)

Film-coating:
Methacrylic acid – ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate
Ferric oxide yellow
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years**.**

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister (PVC/Aluminium).
Blister (PVC/PVDC Aluminium)

Pack sizes:
Blisters: 10, 20, 28, 30, 50, 56, 60, 90, 100 gastro-resistant tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/189/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th July 2011
Date of last renewal: 5th may 2016

10 DATE OF REVISION OF THE TEXT

July 2024