

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nuasa 75 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

Each tablet contains 45 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

White gastro-resistant coated tablets, round and biconvex, without break-score.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- For decreasing the risk of myocardial infarction in patients with stable and unstable angina pectoris.
- Secondary prophylaxis after myocardial infarction.
- Prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery.
- For the secondary prevention of transient ischaemic attacks (TIA) and stroke provided that intracerebral haemorrhages have been ruled out.

Nuasa 75 mg gastro-resistant tablets are not recommended for the use in emergency situations but are restricted to chronic treatment only.

4.2 Posology and method of administration

Posology

Decreasing the risk of myocardial infarction in patients with stable and unstable angina pectoris:

75 to 150 mg per day

Secondary prophylaxis after myocardial infarction

75 to 150 mg per day

Prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery

100 to 300 mg per day

Secondary prevention of transient ischaemic attacks (TIA) and stroke

75 to 150 mg per day

ASA is suitable for long-term treatment with the lowest effective dose.

Elderly patients

ASA should be used with caution in elderly patients as they are at higher risk for adverse events.

Paediatric population

ASA should not be given to children below 16 years of age because of safety concerns (see section 4.4).

Method of administration

The gastro-resistant tablets should be swallowed as a whole with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients, to other salicylates or to related substances.
- Hypersensitivity to other salicylates or other nonsteroidal analgesics / antirheumatics (NSAIDs).
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Active, or history of recurrent peptic and intestinal ulcer and/or gastric/intestinal bleeding/haemorrhage or history of gastrointestinal bleeding.
- Other kinds of bleeding such as cerebrovascular haemorrhages.
- Haemorrhagic diathesis, thrombocytopenia, haemophilia.
- Severe renal insufficiency.
- Severe hepatic impairment.
- Doses > 100 mg/day during the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Nuasa 75 mg gastro-resistant tablets are not suitable for anti-inflammatory, analgesic or antipyretic use.

Caution is required in cases of

- other allergies (e.g. accompanied by skin reactions, pruritus, urticaria),
- asthma bronchiale, hay fever, swelling of the mucosa in the nose (nasal polyps), chronic airway diseases. ASA may trigger asthma or bronchospasm,
- concomitant therapy with antithrombotic medicines (e.g. coumarin derivatives, heparin - except for low-dose heparin treatment),
- genetically determined glucose-6-phosphate dehydrogenase deficiency (haemolytic anaemia),
- gastrointestinal complaints (e.g. gastritis),
- history of gastric or duodenal ulcers ,
- disorders of the renal and/or hepatic function.

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs including acetylsalicylic acid. The risk of GI bleeding, ulceration or perforation is higher with increasing doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Serious skin reactions, including Erythema exsudativum multiforme, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Before scheduled surgical procedures (even minor procedures such as dental surgery), the antithrombotic effect of ASA needs to be considered. Prolongation of bleeding time may occur.

Additional intake of other salicylates or other non-steroidal anti-inflammatory medicines should be avoided.

In taking ASA in higher doses for many years, kidney damage may not be excluded. The renal function should be monitored regularly.

Taking ASA prior to antithrombotic treatment may increase the risk of bleeding. These patients should therefore be monitored for symptoms of outer (e.g. bruising) or inner bleeding. In low doses, acetylsalicylic acid reduces uric acid excretion. This may precipitate gout attacks in predisposed patients.

This medicine contains lactose monohydrate. Patients with a rare congenital galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Elderly patients

ASA should be used with caution in elderly patients as they are at higher risk for adverse events.

Paediatric population

ASA is not recommended for use in children and adolescents under 16 years since life-threatening complications (Reye's syndrome) have been observed in isolated cases in this age group. If ASA is to be given to children and adolescents under 16 years, the expected benefit of treatment has to clearly outweigh the possible risks.

4.5 Interaction with other medicinal products and other forms of interaction

ASA may increase the risk for:

- undesirable effects of non-steroidal anti-inflammatory medicines and antirheumatics,
- for undesirable effects of methotrexate (due to decreased renal clearance),
- gastrointestinal bleeding during concomitant use of alcohol,
- gastrointestinal bleeding and ulceration during concomitant use of corticosteroids,
- hepatotoxicity during concomitant use of ciclosporin,
- bleeding including upper gastrointestinal bleeding during concomitant use of SSRI (selective serotonin reuptake inhibitors).

The concomitant intake of ASA may increase the effects of the following substances:

- digoxin, barbiturates and lithium (due to increased blood levels)
- anticoagulant and antithrombotic drugs (e.g. coumarin derivatives, heparin, dipyridamole, sulfinpyrazone); there is an increased risk of bleeding,
- sulfonamide derivatives (increased hypoglycaemic effect),
- valproic acid.

The concomitant intake of ASA may decrease the effects of the following substances:

- the effect of spironolactone and furosemide,
- the effect of uricosuric agents (probenecid, sulfinpyrazone),
- the effect of antihypertensive agents.

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA 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).

Non-absorbable complexes may be produced by concomitant intake of tetracyclines. Therefore an interval of at least 1-3 hours should be observed between the intakes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Low doses (up to 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require special monitoring, are 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/d and above also apply for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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%, to 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 oligohydramnios;

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

The active substance acetylsalicylic acid and its metabolites are excreted into breast milk in small amounts. As harmful effects on the child have not been established so far, cessation of breast feeding is not required during the short-term administration of daily doses of up to 150 mg. During long-term administration or the intake of higher doses (more than 150 mg daily), the patients should be weaned off.

4.7 Effects on ability to drive and use machines

ASA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Rare: prolongation of bleeding time, thrombocytopenia.

Immune system disorders

Rare: hypersensitivity reactions such as bronchospasm and skin reactions (including Erythema exsudativum multiforme in isolated cases), possibly accompanied by a decrease in blood pressure, dyspnoea, anaphylactic reactions (including shock) and angioneurotic oedema, especially in asthmatics.

Nervous system disorders

Very rare: intracranial haemorrhage.

Ear and labyrinth disorders

Rare: the intake of higher doses may produce vertigo and tinnitus.

Respiratory, thoracic and mediastinal disorders

Rare: triggering of asthma attacks.

Gastrointestinal disorders

Rare: nausea, vomiting, occult gastrointestinal bleeding, which - in rare cases - may lead to iron deficiency; gastrointestinal ulcers with serious bleeding and gastric or duodenal perforation.

Hepatobiliary disorders

Rare: the intake of higher doses for long periods may lead to liver damage.

Renal and urinary disorders

Rare: the intake of higher doses for long periods may lead to kidney damage.

4.9 Overdose

In case of ASA-intoxication, gastrointestinal irritations such as nausea, vomiting and abdominal pain are predominant; vertigo, headache, confusion, tinnitus and hyperventilation with respiratory alkalosis may further occur. Subsequently, CNS depression, hyperpyrexia, respiratory and metabolic acidosis, toxic circulatory collapse and kidney failure, brain and lung oedema and coma may occur. In children hypoglycaemia is possible.

ASA intoxication requires symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin

ATC code: B01AC06

Mechanism of action

The antithrombotic effect of ASA is based on the inhibition of thromboxane A₂-synthesis in thrombocytes.

Pharmacodynamic effects

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release ASA dosing (81mg), a decreased effect of ASA 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.

Clinical efficacy and safety

New clinical studies show that the antithrombotic effect of ASA is already present in very low doses.

ASA is also used in the treatment of the Kawasaki syndrome which occurs rarely. The corresponding dosages are given in actual specialised literature.

5.2 Pharmacokinetic properties

After the application as gastro-resistant formulation, ASA is absorbed in the duodenum. Maximum plasma levels are achieved 3 hours after administration. ASA is hydrolysed enzymatically to salicylic acid in the intestinal mucosa, but predominantly in the liver. Furthermore, salicylic acid is glucuronised in the liver.

ASA gastro-resistant tablets are bioequivalent with a hydrous solution of ASA; due to the particular pharmaceutical form, the half-life is prolonged from 2 to 4 hours.

Excretion of salicylic acid (85 % in alkaline and 10 % in acid urine) as well as its conjugates and derivatives happens mainly renal.

5.3 Preclinical safety data

Preclinical results of experiments were achieved after oral, nasal, subcutaneous and intravenous application in mice, rats, guinea pigs, rabbits, and dogs.

In chronic toxicity experiments using human therapeutic doses of ASA, no significant differences compared with the control group were noticed.

In vitro investigations showed no mutagenic potential of ASA.

Studies in mice and rats proved no cancerogenic potential of ASA.

Reproduction toxicology:

In animal experiments (rat, dog) using higher doses of ASA, teratogenic effects occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Colloidal anhydrous silica

Potato starch

Talc

Triacetin

Methacrylic acid-ethylacrylate copolymer (1:1) dispersion 30%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

PVC / aluminium blisters with 30, 90 and 500 tablets per package.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Uniphar plc
Citywest Business Park
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1455/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 2011

10 DATE OF REVISION OF THE TEXT