Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nu-seals 75 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Aspirin (Acetylsalicylic acid) 75mg.

Excipients withknowneffect
Benzyl Alcohol 0.128mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Smooth, white tablets printed with '75' in red.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aspirin has an antithrombotic action, mediated through inhibition of platelet activation, which has been shown to be useful in secondary prophylaxis following myocardial infarction, and in patients with unstable angina or ischaemic stroke.

Nu-Seals 75 is indicated wherever prolonged dosage of aspirin is required. The special coating resists dissolution in gastric juice, but will dissolve readily in the relatively less acid environment of the duodenum. Owing to the delay that the coating imposes on the release of the active ingredient, Nu-Seals 75 is unsuitable for the short-term relief of pain.

4.2 Posology and method of administration

Posology

Adults
Antithrombotic action: The usual dose is 75mg, daily. When rapid absorption is required (e.g., following acute myocardial infarction), two tablets (150mg) should be taken together and chewed.

Elderly
As for adults. In general, aspirin should be used with particular caution in elderly patients who are more prone to adverse events.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). Treatment should be reviewed at regular intervals.

Paediatric population
Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk (see section 4.4).

Methodofadministration
For oral administration.

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 heart failure.

Doses >100 mg/day during the third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

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.

The use of Nu-Seals 75 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.

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 Nu-Seals 75, 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 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.

Aspirin can reduce uric acid excretions and so should be used with care in patients with gout or a history of gout.

Aspirin should be used with caution in patients with 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. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Nu-seals 75 contains benzyl alcohol. High volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of benzyl alcohol accumulation and toxicity (metabolic acidosis). Benzyl alcohol may also cause allergic reactions.

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

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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.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects.

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, Stevens-Johnson 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. Nu-Seals 75should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 therapy 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.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin may enhance the effects of anticoagulants, antiplatelet agents and fibrinolytics leading to increased risk of bleeding.

Concomitant use of alcohol with aspirin may increase the risk of gastrointestinal bleeding.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Salicylates inhibit the uricosuric effect of uricosuric drugs.

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

<u>Care should be taken in patients treated with any of the following drugs as interactions have been reported:</u>

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

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

Anti-hypertensives: reduced anti-hypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: decreased elimination of lithium.

Methotrexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxity with NSAIDs.

Gold: risk of increased hepatotoxicity with aspirin.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAIDs and metabolites.

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.

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 aspirin and corticosteroids are co-administered (see Section 4.4).

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

Other NSAIDs: Avoid concomitant use with other NSAIDs.

Ibuprofen: Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin 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).

Phenytoin and valproate: The effect of phenytoin and valproate may be enhanced by aspirin. However, no special precautions are needed.

Aspirin can interfere, to varying degrees, with some urine tests for catecholamines, dopa, glucose, ketones, hippuric acid, homogentisic acid, homovallinic acid, 17-hydroxycorticosteroids, 5-hydroxyindoleacetic acid, urine pregnancy tests and with some serum or plasma tests for albumin, barbiturates, calcium, propylthiouracil, tyrosine and uric acid.

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 and including 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 above 100 mg/day and up to 500mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendation 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 prostaglandin synthesis inhibitor has been shown to results 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, acetylsalicylic acid 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, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to acetylsalicylic acid for several days from gestational week 20 onward. Acetylsalicylic acid 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, which may progress to renal failure with oligohydroamniosis;

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 higher than 100 mg/day is contraindicated during the third trimester of pregnancy (see section 4.3). Doses up to and including 100 mg/day may only be used under strict obstetric monitoring.

*Breast-feeding:*As aspirin is secreted into breast milk, Nu-Seals 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

Not applicable.

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	*Not Known:* Bleeding disorders Anaemia[1] Thrombocytopenia	
Immune system disorders	*Not Known:* Hypersensitivity reactions including skin rashes, urticaria, angioedema,	

	asthma, bronchospasm and anaphylaxis. Bullous reactions including Stevens-Johnson and toxic epidermal necrolysis syndrome	
Nervous system disorders	*Not Known:* Cerebral haemorrhage	
Ear and labyrinth disorders	*Not Known:* Tinnitus	
Cardiac disorders	*Not Known:* Cardiac failure	
Vascular disorders	*Not Known:* Hypertension Haemorrhages[2] Haematoma[2]	
Respiratory thoracic and mediastinal disorders	*Not Known:* Epistaxis Haemoptysis	
Gastrointestinal disorders[3]	*Not Known:* Peptic ulcers[4] GI Perforation[4] GI Bleeding[4] Nausea Vomiting Diarrhoea Flatulence Constipation Dyspepsia Abdominal pain Melaena Haematemesis Ulcerative stomatitis Exacerbation of colitis Exacerbation of Crohn's disease Gastritis Gastrointestinal ulcer	
Skin and subcutaneous tissue disorders	*Not Known:* Purpura Ecchymoses	
Renal and urinary disorders	*Not Known:* Haematuria Urate kidney stones	
General disorders and administration site disorders	*Not Known:* Oedema	
Investigations	*Not Known:* Bleeding time prolonged	
Hepatobiliary disorders	*Not Known:* Transaminases increased	

[1]May occur following chronic GI blood loss or acute haemorrhage
[2]May occur in various organ systems and may be fatal
[3]The special coating of Nu-Seals helps to reduce the incidence of side effects resulting from gastric irritation.
[4]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 principle 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, hypoprothrombina, thrombocytopenia, increased INR/PTR, intravascular coagulation, dehydration, oliguria, renal failure, GI bleeding non-cardiogenic pulmonary oedema, asphyxation, 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: Salicylic Acid & Derivatives
ATC code: B01A C06

Aspirin has an antithrombotic action which is mediated through inhibition of platelet activation.

Nu-Seals 75 tablets have a gastro-resistantcoat sandwiched between a sealing coat and a top coat. The gastro-resistantcoat is intended to resist gastric fluid whilst allowing disintegration in the intestinal fluid.

Owing to the delay that the coating imposes on the release of the active ingredient, Nu-Seals 75 is unsuitable for the short-term relief of pain.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin 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 aspirin dosing (81mg), a decreased effect of aspirin 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

In a bioequivalence study comparing the pharmacokinetics of the 300mg Nu-Seals aspirin product with 4 x 75mg presentation in human volunteers, measures such as terminal phase half-life, area-under-the-curve and peak plasma concentrations were recorded on days 1 and 4. On day 1 salicylate reached a peak plasma concentration of between 10.34 and 31.57 mcg/ml and between 11.76 and 27.47 mcg/ml for the 300mg and 75mg tablets respectively. Time to peak concentration ranged from 4 to 8 hours and from 3 to 6 hours respectively. AUC 0-∞ ranged from 54.0 to 131.2 and from 64.3 to 137.6 h.mcg/ml respectively. The terminal phase half-life ranged from 1.33 to 2.63 hours and from 1.47 to 2.59 hours respectively. On day 4, Cmax varied from 15.01 to 48.97 mcg/ml for the 300mg tablet and from 11.26 to 60.21 mcg/ml for 4 x 75mg tablets. Tmax ranged from 4 to 8 hours and from 3 to 8 hours, whilst AUC 0-8range from 89.8 to 297.4 h.mcg/ml and from 61.5 to 293 h.mcg/ml respectively.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Polyethylene Glycol 3350
Talc
Emulsion silicone
Hypromellose
Propylene Glycol
Benzyl alcohol
Methacrylic acid-ethyl acrylate (1:1) copolymer dispersion 30 per cent
Printing ink containing shellac, iron oxide (E172), isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide (E527) and simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

As packaged for sale:
Blisters: Three years.
HDPE containers: Two Years.

After first opening of HDPE containers: Use within 8 weeks of opening.

6.4 Special precautions for storage

Do not store above 25°C.

Blister packs: Store in the original package in order to protect from moisture.

HDPE containers: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

UPVC/Aluminium foil blister packaging, pack sizes 28 and 56.
High-density polyethylene (HDPE) round plastic container with a plastic child-resistant tamper-evident screw cap, pack size 100.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharma (Ireland) Limited
United Drug Distributors, United Drug House
Magna Business Park, Magna Drive
Citywest
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2325/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 1997
Date of last renewal: 23 April 2007

10 DATE OF REVISION OF THE TEXT

September 2025