SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nu-Seals 300
Aspirin 300mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Acetylsalicylic Acid 300mg

Excipients with known effect
Propylene Glycol 0.895mg per tablet
Benzyl Alcohol 0.334mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White tablet, with 300 printed in red on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aspirin has analgesic, antipyretic and anti-inflammatory actions. It can also be used for the secondary prevention of thrombotic cerebrovascular or cardiovascular disease and following by-pass surgery in adults (see below).

Aspirin has an anti-thrombotic 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 including cerebral transient attacks.

Nu-Seals 300 is indicated wherever high and 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 duo¬denum. Owing to the delay that the coating imposes on the release of the active ingredient, Nu-Seals 300 is unsuitable for the short-term relief of pain.

4.2 Posology and method of administration

Posology

Adults
Analgesic, antipyretic and anti-inflammatory actions: The usual dose of aspirin is 300-900mg repeated three to four times daily according to clinical needs. In acute rheumatic disorders the dose is in the range of 4-8 g daily, taken in divided doses.

Antithrombotic action: Patients should seek the advice of a doctor before commencing therapy for the first time. The usual dosage, for long-term use following myocardial infarction, transient ischaemic attack, or in patients with unstable angina, is 75-150mg once daily. In some circumstances a higher dose may be appropriate, especially in the short term, and up to 300mg a day may be used on the advice of a doctor.

Antithrombotic action: The risk-benefit ratio has not been fully established.

Elderly
Analgesic, antipyretic and anti-inflammatory actions: As for adults, the elderly are more likely to experience gastric side-effects and tinnitus.

Paediatric population
Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease). See 'Special Warnings and Special Precautions for Use'.

Method of administration
For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance 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 or a history of peptic ulceration.

Third trimester of pregnancy (see section 4.6).

In women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

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 aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

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

Before commencing long-term aspirin therapy for the management of cerebrovascular or cardiovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.

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.

Salicylates should be used with caution in patients with inflammatory bowel disease or coagulation abnormalities as they may also induce gastro-intestinal haemorrhage, occasionally major.

They 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 should be used with caution in patients with impaired renal or hepatic function (avoid if severe), or in patients who are dehydrated.

Nu-seals 300mg 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.

Patients with hypertension should be carefully monitored.

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

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.

Salicylates may enhance the effect of oral hypoglycaemic agents, phenytoin and sodium valproate. They inhibit the uricosuric effect of probenecid and may increase the toxicity of sulphonamides.

Angiotensin converting enzyme inhibitors (ACE) in combination with acetylsalicylic acid at higher doses lead to decreased glomerular filtration via inhibition of vasodilatory prostaglandins and therefore, decreased antihypertensive effect.

Diuretics can increase the risk of nephrotoxicity of NSAIDs via decreased renal prostaglandin synthesis.

Aspirin may potentiate the effect of heparin and increases the risk of bleeding with oral anticoagulants, antiplatelet agents and fibrinolytics.

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.

Concurrent use of aspirin and other NSAIDs should be avoided. Use of two or more NSAID preparations increases the risk of serious gastrointestinal haemorrhage.

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

In large doses, salicylates may also decrease insulin requirements.

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

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).

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

Methotrexate: decreased elimination of methotrexate.

Cyclosporin, tacrolimus: increased risk of nephrotoxicity with NSAIDs.

Gold: risk of increased hepatotoxicity with aspirin.

Thiopental: Aspirin may potentiate the effects of thiopental anaesthesia.

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.

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

4.6 Fertility, pregnancy and lactation

Fertility: Findings from a variety of animal models with a number of NSAIDs including aspirin indicate that these active substances block blastocyst implantation which may have an impact on female fertility (see section 4.4).

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 500 mg/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 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 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 excreted 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

None known.

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

Blood and lymphatic system disorders	*Not known:* Anaemia[1] Bleeding disorders[2] Thrombocytopenia
Immune system disorders	*Not known:* Hypersensitivity reactions including skin rashes, urticaria, angioedema, asthma, bronchospasm and anaphylaxis.
Nervous system disorders	*Not known:* Cerebral haemorrhage
Ear and labyrinth disorders	*Not known:* Tinnitus
Vascular disorders	*Not known:* Haematoma Haemorrhage
Respiratory thoracic and mediastinal disorders	*Not known:* Epistaxis Haemoptysis
Gastrointestinal disorders	*Not known:* Gastrointestinal irritation Nausea Vomiting Dyspepsia Gastritis Gastrointestinal erosions Gastrointestinal ulcer Gastrointestinal bleeding
Skin and subcutaneous tissue disorders	*Not known:* Purpura Ecchymoses
Renal and urinary disorders	*Not known:* Urate kidney stones Haematuria
Investigations	*Not known:* Bleeding time prolonged[2] Transaminases increased

[1] may occur following chronic gastrointestinal blood loss or acute haemorrhage.
[2] fatalities have occurred.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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.

With the gastro-resistant formulation, peak plasma levels may not occur for up to 12 hours.

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

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, 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 to 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.

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.

Uncommon features include tachypnoea, diaphoresis, haematemesis, hyperpyrexia, hypoglycaemia or hyperglycaemia (more common in younger children), increased ketone levels, hypokalaemia, hypernatraemia, hypoprothrombinaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, dehydration, oliguria, renal failure, GI bleeding, non-cardiogenic pulmonary oedema, asphyxiation, respiratory arrest, dysarrhythmias, hypotension, PT prolongation and cardiovascular arrest.

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

Management
Consider administration of activated charcoal if an adult present within one hour of ingestion of 125 mg/kg or more. Where the practical expertise exists, gastric lavage can be considered in adults presenting within 1 hour of a potentially life-threatening overdose (500 mg/kg salicylate or more), providing the airway can be protected. The plasma salicylate concentration should be measured for patients who have ingested >125 mg/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 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: N02B A01and B01A C06

Aspirin has analgesic, antipyretic and anti-inflammatory actions.

It also has antithrombotic action, which is mediated through inhibition of platelet activation.

Nu-Seals 300 tablets have a gastro-resistant coat sandwiched between a sealing coat and a topcoat. The gastro-resistant coat 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 300 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 hours before or within 30 minutes after immediate release aspirin (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 300 mg product with 4 x 75 mg 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 27.47mcg/ml for the 300 mg and 75 mg tablets respectively. Time to peak concentration ranged from 4 to 8 hours and from 3 to 6 hours respectively. AUC 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 C_{max} varied from 15.01 to 48.97 mcg/ml for the 300 mg tablet and from 11.26 to 60.21 mcg/ml for 4 x 75 mg tablets. T_{max} ranged from 4 to 8 hours and from 3 to 8 hours, whilst AUC ranged from 89.8 to 297.4 h.mcg/ml and from 61.5 to 293.4 h.mcg/ml respectively.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber in addition to that summarised in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch

Hypromellose

Talc

Methacrylic acid – ethyl acrylate (1:1) copolymer dispersion 30 per cent

Polyethylene Glycol 3350

Propylene Glycol

Benzyl Alcohol

Emulsion silicone

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

3 years

6.4 Special precautions for storage

Do not store above 25°C. Keep containers tightly closed.

6.5 Nature and contents of container

White HDPE bottles with polypropylene, child resistant caps with a liner containing 100 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Limited
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SN15 2BB

8 MARKETING AUTHORISATION NUMBER(S)

PL 16853/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

07/05/2025