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 300 mg

3 PHARMACEUTICAL FORM

White, gastro-resistant tablets, coded “300” in red or “GP” in black

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 (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 duodenum. 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

Nu-Seals 300 is for oral administration to adults only.

*Analgesic, antipyretic and anti-inflammatory actions:* The usual dose of aspirin is 300-900 mg 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 75-150 mg once daily. In some circumstances a higher dose may be appropriate, especially in the short term, and up to 300 mg a day may be used on the advice of a doctor.

*The elderly: Analgesic, antipyretic and anti-inflammatory actions:* As for adults. The elderly are more likely to experience gastric side-effects and tinnitus. *Antithrombotic action:* The risk-benefit ratio has not been fully established.

*Children:* Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki’s disease). See ‘Special Warnings and Precautions for Use’.

4.3 Contraindications

Hypersensitivity to aspirin. Hypoprothrombinaemia, haemophilia and active peptic ulceration or a history of peptic ulceration.

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).

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 a history of peptic ulceration or coagulation abnormalities. They may also induce gastro-intestinal haemorrhage, occasionally major.

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

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

Patients with hypertension should be carefully monitored.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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).

### 4.6 Pregnancy and lactation

**Pregnancy:** Although clinical and epidemiological evidence suggests the safety of aspirin for use in pregnancy, caution should be exercised when considering use in pregnant patients. Aspirin has the ability to alter platelet function and there may be a risk of haemorrhage in infants whose mothers have consumed aspirin during pregnancy. Prolonged pregnancy and labour, with increased bleeding before and after delivery, decreased birth weight and increased rate of stillbirth have been reported with high blood salicylate levels. With high doses there may be premature closure of the ductus arteriosus and possible persistent pulmonary hypertension in the newborn. Analgesic doses of aspirin should be avoided during the last trimester of pregnancy.

**Lactation:** As aspirin is excreted in 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

Gastrointestinal irritation is common in patients taking aspirin preparations, and nausea, vomiting, dyspepsia, gastritis, gastrointestinal erosions and ulceration have been reported. Anaemia may occur following chronic gastrointestinal blood loss or acute haemorrhage.

Aspirin prolongs bleeding time, and bleeding disorders, such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, gastrointestinal bleeding, haematoma and cerebral haemorrhage have occasionally been reported. Fatalities have occurred.

Hypersensitivity reactions include skin rashes, urticaria, angioedema, asthma, bronchospasm and rarely, anaphylaxis.

Other side effects: urate kidney stones and tinnitus.
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.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

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 haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiogenic pulmonary oedema.

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

Management

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (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

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 top coat. 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 27.47 mcg/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

None.

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
HDPE bottles with screw caps containing 14, 56, 100 or 500 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Ltd
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For Aspirin 300mg Gastro-resistant Tablets trading as:

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2006

10 DATE OF REVISION OF THE TEXT