Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nu-Seals 75mg Gastro-Resistant Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Printing ink contains Ponceau 4R red (E124)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant Tablet.

Product imported from the UK:

White, circular, tablet with '75' printed 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

Undesirable effects may be minimised by using the shortest duration necessary to control symptoms *(see section 4.4).*

Nu-Seals 75 is for oral administration to adults only.

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

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

The lowest dose compatible with adequate safe clinical control should be employed *(see section 4.4).* Treatment should be reviewed at regular intervals.

Children:
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).*

4.3 Contraindications

Hypersensitivity (e.g. bronchospasm, rhinitis, urticaria) to aspirin or to non-steroidal anti-inflammatory drugs. Hypoprothrombinaemia, haemophilia, cerebral haemorrhage and active peptic ulceration.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurring peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms *(see section 4.2, and GI and cardiovascular risks below).*

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.

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for acetylsalicyclic acid.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with acetylsalicyclic acid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

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.

In patients with renal, cardiac or hepatic impairment, caution is required 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 regular thereafter.

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.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including aspirin. 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 should be used with caution in patients with impaired renal function or hepatic function (avoid if severe), or in patients who are dehydrated. Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects. Patients with hypertension should be carefully monitored.

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

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

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal *(see section 4.2).*

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 advisedin patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin *(see section 4.5).*

When GI bleeding or ulceration occurs in patients receiving Nu-Seals, 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).*

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Anti-hypertensives: reduced anti-hypertensive effects.

Diuretics: reduced diuretics effect. Diuretics can increase the risk of nephrotoxicity or 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 nephrotoxicity with NSAIDs.

Other NSAIDs: avoid concomitant use with other NSAIDs.

Corticosteroids: increased risk of gastrointestinal bleeding.

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

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

Oral hypoglycaemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Antacids: patients using enteric coated aspirin should be advised against ingesting antacids simultaneously to avoid premature drug release.

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).*

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 Fertility, pregnancy and lactation

Usage in pregnancy:

Aspirin does not appear to have teratogenic effects. However, prolonged pregnancy and labour, with increased bleeding before and after delivery, decreased birth weight and increased rate of stillbirth were reported with high blood salicylate levels. Routine use should be avoided during pregnancy.

Usage in nursing mothers:

As aspirin is excreted in breast milk, Nu-Seals should not be taken by patients who are breast-feeding.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Salicylates may induce hypersensitivity, asthma, urate kidney stones, chronic gastro-intestinal blood loss, tinnitus, nausea and vomiting. The special coating of Nu-Seals 75 helps to reduce the incidence of side-effects resulting from gastric irritation.

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature.

Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur *(see section 4.4).* Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease *(see section 4.4 – Special warnings and precautions for use)* have been reported following administration. Less frequently, gastritis has been observed.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) *(see section 4.4).*

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

4.9 Overdose

Overdosage produces dizziness, tinnitus, sweating, nausea and vomiting, confusion and hyperventilation. Gross overdosage may lead to CNS depression with coma, cardiovascular collapse and respiratory depression.

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. Treatment of overdosage consists of gastric lavage and forced alkaline diuresis. Haemodialysis may be necessary in severe cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aspirin has an antithrombotic action which is mediated through inhibition of platelet activation. Nu-Seals 75 tablets have an enteric coat sandwiched within a sugar coat and a top coat. The enteric 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 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 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.

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 31.57mcg/ml and between 11.76 and 27.47mcg/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 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 48.97mcg/ml for the 300mg tablet and from 11.26 to 60.21mcg/ml for 4 x 75mg tablets. Tmax 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 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
Hypromellose
Talc
Methacrylic acid-ethyl acrylate (1:1) copolymer dispersion 30%
Macrogol 3350
Propylene glycol

Benzyl alcohol
Silicone emulsion
Edible printing ink (Ponceau 4R red (E124) and shellac).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister packs containing 56 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/074/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2001

Date of last renewal: 27 July 2006

10 DATE OF REVISION OF THE TEXT

April 2011