Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anadin Maximum Strength Hard Capsules Aspirin 500mg, caffeine 32mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Aspirin (Acetylsalicylic Acid)	500.0 mg
Caffeine Anhydrous	32.0 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, hard.
Size 0 hard gelatin capsules with green caps and yellow bodies, containing a white powder/granule mixture. 'Anadin 500' is printed longitudinally in black on each half.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of headaches, neuralgia, rheumatic, period and dental pain, and the symptoms of colds and flu.

4.2 Posology and method of administration

Posology
Adults and children over 16 years:
1 capsule every three to four hours
Do not exceed 8 capsules in 24 hours

Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.

Elderly:
Non-steroidal anti-inflammatory drugs should be used with particular caution in elderly patients who are prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also Section 4.4.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Method of Administration: Oral.

4.3 Contraindications

• Use in patients hypersensitive (e.g. bronchospasm, rhinitis, urticaria) to the active ingredients or any other constituents.
• 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).
• Use in patients with bleeding disorders.
• Use in patients with severe heart failure.
• Use in patients who are breast feeding or in the last 3 months of pregnancy.
• Use in children under 16 years.

4.4 Special warnings and precautions for use

• The use of Anadin Maximum Strength capsules with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

• In patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, aspirin is known to rarely cause haemolytic anaemia.
• 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 if 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, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
• When GI bleeding or ulceration occurs in patients receiving Anadin Maximum Strength capsules, 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 sections 4.8 – undesirable effects).
• Patients with a history of, inflammatory bowel disease, coagulation disorders, or asthma should consult a doctor before using this product.
• Aspirin may induce asthmatic attacks in hypersensitive patients.
• 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 (e.g. Kawasaki's disease).
• Prolonged use, except under medical supervision, can be harmful. If symptoms persist, the physician should be consulted.
• If you are taking any other medication or are under the care of a doctor you should consult the physician before using.
• 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 regularly thereafter.
• As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.
• 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.
• 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.
• 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. Anadin Maximum Strength capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
• Caution should be exercised in patients with dehydration.
• If symptoms persist for more than 3 days, review patients treatment and discontinue treatment if no benefit is seen.

• **Cardiovascular and cerebrovascular effects:**
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). There are insufficient data to exclude such a risk for aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

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).

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

Anti-coagulants: **It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision as NSAIDs may enhance the effects of anti-coagulants.**
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 nephrotoxicity with NSAIDs

Other NSAIDs: avoid concomitant use of two or more NSAIDs, as this may increase the likelihood of GI side effects

Corticosteroids: increased risk of gastrointestinal bleeding and ulceration.

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.

Metoclopramide: increased rate of absorption of aspirin.

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

Valproate: the effect of valproate may be enhanced by aspirin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There is clinical and epidemiological evidence of safety of aspirin in pregnancy, but it may prolong labour and contribute to maternal and neonatal bleeding, and so should not be used in late pregnancy.

During the first and second trimester of pregnancy, aspirin should not be given unless clearly necessary.

Lactation
Aspirin appears in breast milk and regular high doses may affect neonatal clotting. Not recommended while breast feeding due to possible risk of Reye's Syndrome as well as neonatal bleeding due to hypoprothrombinaemia.

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Reduced ability of the blood to clot, which may result in easy bruising or bleeding.

Aspirin may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions in susceptible individuals.

The most common observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal 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.

Other side effects include asthma, renal urate calculi formation, bleeding and tinnitus. Aspirin may precipitate gout in susceptible individuals.

Very rarely Anaemia, Aplastic Anaemia, Pancytopenia.

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

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).

Possible risk of Reye's Syndrome in children under 16 years.

High doses of caffeine can cause tremor and palpitations.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 dose less than 100mg/kg are unlikely to cause serious poisoning.

Aspirin
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 four years old. In children aged four 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, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

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

Caffeine
Common features include CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions.
Cardiac Symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include abdominal or stomach pains.
Other symptoms of overdosage, associated with the caffeine component, include diuresis and facial flushing.

Management

Aspirin
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 alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intraveneous 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 or over 70 years have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine
Treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by intravenous administration of diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02BE51
Pharmacotherapeutic group: Other analgesics and antipyretics

Aspirin is a non-steroidal anti-inflammatory agent. It has analgesic antipyretic and anti-inflammatory properties.

Caffeine increases the pain relieving effect of the product

Aspirin

Mechanisms of action/effect
Salicylates inhibit the activity of the enzyme cyclo-oxygenase to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although many of the therapeutic effects may result from inhibition of prostaglandin synthesis (and consequent reduction of prostaglandin activity) in various tissues, other actions may also contribute significantly to the therapeutic effects.

Analgesic
Produces analgesia through a peripheral action by blocking pain impulse generation and via a central action, possibly in the hypothalamus.

Anti-inflammatory (Nonsteriodal)
Exact mechanisms have not been determined. Salicylates may act peripherally in inflamed tissue probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other mediators of the inflammatory response.

Antipyretic
May produce antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased cutaneous blood flow, sweating and heat loss.
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.

Caffeine

Mechanisms of action/effect

Central nervous system stimulant - caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

Analgesia adjunct
Caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhancing pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

5.2 Pharmacokinetic properties

ASPIRIN

Absorption and fate

Absorption is generally rapid and complete following oral administration. It is largely hydrolysed in the gastrointestinal tract, liver and blood to salicylate which is further metabolised primarily in the liver.

CAFFEINE

Absorption and fate

Caffeine is completely and rapidly absorbed after oral administration with peak concentrations occurring between 5 and 90 minutes after dose in fasted subjects. There is no evidence of presystemic metabolism. Elimination is almost entirely by hepatic metabolism in adults.

In adults, marked individual variability in the rate of elimination occurs. The mean plasma elimination half life is 4.9 hours with a range of 1.9 - 12.2 hours. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine. The major metabolites are 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6 formylamino-3-methyluracil (AMFU).

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Dimethicone
Quinoline yellow (E104)
Titanium Dioxide (E171)
Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)

Patent blue V (E131)

Printing Ink
Shellac
Iron oxide, black (E172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original package.

6.5 Nature and contents of container

Cartons containing UPVC/Aluminium foil blister strips - 8, 10, 12, 16, 20, 24, 30 and 32.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Haleon Ireland Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/148/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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