Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anadin Analgesic Film-coated Tablets Aspirin 325mg Caffeine 15mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Acetylsalicylic acid (aspirin)	325.0 mg
Caffeine	15.0 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White capsule shaped, film coated tablets.

The tablets have '325/15' engraved on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of pain of headache, neuralgia, rheumatic pain, period pain, dental pain, toothache, and the relief of symptoms of the common cold.

4.2 Posology and method of administration

Oral

Adults and Adolescents over 16 years: Take 2 tablets every 4 hours if necessary. Do not exceed 12 tablets in any 24 hour period.

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 more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also Section 4.4.

4.3 Contraindications

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to Anadin Analgesic Film-coated Tablets, aspirin or other non-steroidal anti-inflammatory drugs or any of the other constituents.

Children and adolescents under 16 years.

Breast-feeding.

Last-trimester of pregnancy.

Concurrent anti-coagulant therapy.

Patients with severe renal failure.

Intake of more than 15mg methotrexate per week.

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 severe heart failure.

Use in patients with bleeding disorders.

4.4 Special warnings and precautions for use

The use of Anadin Tablets 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 GU 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 Tablets, the treatment should be withdrawn.In patients suffering from severe glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, aspirin is known to rarely cause haemolytic anaemia.

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.

Prolonged use, except under medical supervision, can be harmful. If symptoms persist, the physician should be consulted.

If you are taking any other medications 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. 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.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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).

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, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, includingpossible acute renal failure, which is usually reversible. These interactions should be considered in patients taking Anadin Analgesic Film-coated Tablets concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Metoclopramide: Metoclopramide increases the rate of absorption of aspirin. However, concurrent use need not be avoided.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Acetylsalicylic acid should not be used during the first and second trimester of pregnancy unless clearly necessary. If acetylsalicylic acid is used by a woman during the first and second trimesters, the dose should be kept as low as possible and the duration of use as short as possible. It has been suggested in epidemiological studies that prostaglandin synthesis inhibition in early pregnancy is associated with an increased risk of miscarriage, cardiac malformation and gastroschisis. Animal studies have shown an increased risk of post-implantation loss and various malformations including cardiovascular.

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 the third trimester. There is also the risk of cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction.

Breast-feeding

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.

Fertility

If acetylsalicylic acid is used by a woman attempting to conceive the dose should be kept as low as possible and the duration of use as short as possible. Animal studies have shown an increased risk of pre -implantation loss and various malformations including cardiovascular.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Blood and lymphatic system disorders		Bleeding, Anaemia, Aplastic Anaemia, Pancytopenia
Immune system disorders		Hypersensitivity reactions. Acetylsalicyclic acid may precipitate gout in susceptible individuals.
Ear and labyrinth disorders		Tinnitus
Cardiac disorders		Cardiac failure and oedema have been reported in association with NSAID treatment. High doses of caffeine can cause palpitations.
Vascular disorders		Hypertension
Respiratory, thoracic and mediastinal disorders		Asthma. Acetylsalicyclic acid may precipitate bronchospasm and induce asthma attacks or otherhypersensitivity reactions in susceptible individuals.
Gastrointestinal disorders		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.
Hepatobiliary disorders		There is a possible risk of Reye's Syndrome in children under 16 years.
Skin and subcutaneous tissue disorders	Very rare	Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).
Musculoskeletal and connective tissue disorders		High doses of caffeine can cause tremor
Renal and urinary disorders		Renal urate calculi formation

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 Email: medsafety@hpra.ie

4.9 Overdose

Salicylate poisoning is usually associated with plasma concentrations > 350 mg/l (2.5mmol/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

Absorption
Absorption of non-ionised aspirin occurs in the stomach. Aspirin is largely hydrolysed in the GI tract, liver and blood to salicylate, which is further metabolised primarily in the liver.

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

Metabolism
The main metabolic products for salicylates are the glycine conjugate salicyluric acid, the phenolic glucuronide, the ester glucuronide and the oxidation product gentisic acid.

Caffeine is metabolised almost completely via oxidation, demethylation and acetylation.

Excretion
Aspirin is excreted as salicylic acid as glucuronide conjugates and as salicyluric and gentisic acid.

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

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%.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Maize starch
Calcium stearate
Quinine sulfate

Film Coating:
Macrogol
Hypromellose (Methocel E5)
Hypromellose (Methocel E15)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Packs of 6, 8, 12 and 24 come in blister pack composed of white, opaque, unplasticised polyvinyl chloride and printed aluminium foil, coated on the bright side with heat seal lacquer for sealing to PVC.

Not all pack sizes may be marketed.

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 MARKETING AUTHORISATION HOLDER

Haleon Ireland Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/148/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2023