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: One to two film-coated tablets (325 mg to 650 mg acetylsalicylic acid + 15 mg to 30 mg caffeine) every four to six hours as required. 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

Use in patients hypersensitive to the active ingredients or any other constituents. Patients in whom asthma, bronchospasm, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs).Children and adolescents under 16 years.

- Hepatic failure
- Breast-feeding.
- Last-trimester of pregnancy

- Concurrent anti-coagulant therapy.

- Patients with 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

Serious hypersensitivity reactions or anaphylaxis can occur, bronchospasm may be precipitated in patients suffering from or with a previous history of asthma, allergic disease or nasal polyps.
The use of ANADIN Tablets with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive undesirable effects (see Interactions).

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.

Haematological and haemorrhagic effects can occur and may be severe. Patients should report any unusual bleeding symptoms to their physician.

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.

Doses more than 1 g acetylsalicylic acid daily may precipitate acute haemolytic anaemia in patients with G6PDH deficiency.
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, especially during or immediately after a viral illness. 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, particularly during or immediately after chickenpox, influenza, or other viral infections, unless prescribed by a physician or 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 medications or are under the care of a doctor you should consult the physician before using. Acetylsalicylic acid is known to cause sodium and water retention which may exacerbate hypertension, congestive heart failure and renal impairment. 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. 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. Caution is required in patients who are dehydrated or suffering from diabetes mellitus.

Aspirin can cause gout in patients with low uric acid excretion.

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.
Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.

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

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).

Diuretics and antihypertensive agents: 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, including possible 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 and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels

Lithium: Caffeine can increase the elimination of lithium from the body. Concomitant use is therefore not recommended.

Methotrexate: decreased elimination of methotrexate. The toxicity of methotrexate may be enhanced by concomitant use of acetylsalicylic acid aspirin. In case of concomitant use with acetylsalicylic acid, renal function should be monitored **(see Section 4.3 Contraindications).**

Cyclosporin: increased risk of nephrotoxicity with NSAIDs
Other NSAIDs: avoid concomitant use of two or more NSAIDs as these may increase the risk of adverse effects.
Corticosteroids: increased risk of gastrointestinal bleeding and ulceration
Loop diuretics: Acetylsalicylic acid may reduce their activity due to competition and inhibition of urinary prostaglandins. NSAIDs can cause acute kidney failure, especially in dehydrated patients. If a diuretic is administered simultaneously with acetylsalicylic acid, it is necessary to ensure adequate hydration of the patient and to monitor the kidney function and blood pressure, particularly when starting diuretic treatment.

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

Uricosurics (e.g., probenecid, sulfinpyrazone): Acetylsalicylic acid may reduce their activity due to inhibition of tubular resorption, leading to high plasma levels of acetylsalicylic acid**.**

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

Phenytoin: Acetylsalicylic acid increases its serum levels; serum phenytoin should be well monitored.

Valproate: Acetylsalicylic acid inhibits its metabolism and hence could increase its toxicity; valproate levels should be well monitored.
Co-administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal haemorrhage.

Antacids: Antacids may increase the excretion of acetylsalicylic acid by alkalinization of the urine.

Thrombolytics: There is an increased risk of bleeding. Particularly, treatment with acetylsalicylic acid should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended (see Warnings and Precautions).

4.6 Fertility, pregnancy and lactation

Pregnancy
Not recommended for use during pregnancy. This medicine is contraindicated during the third trimester of pregnancy (see Contraindications).

From the 20th week of pregnancy onward, Anadin Analgesic 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, Anadin Analgesic should not be given unless clearly necessary. If Anadin Analgesic 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 Anadin Analgesic for several days from gestational week 20 onward. Anadin Analgesic 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 (see above);

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, Anadin Analgesic is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

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.

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.

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. However, no accurate data is available on when the reversibility of fertility effects occur after the treatment is suspended. Caution should be exercised when used by women who are planning on becoming pregnant.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Adverse events are more likely to occur with increasing dose and duration of use.

Acetylsalicylic acid

MedDRA SOC	**Adverse Reaction**	**Frequency**
Gastrointestinal disorders	Nausea, vomiting, dyspepsia. Gastrointestinal ulceration, gastrointestinal haemorrhage and gastritis. Peptic ulcers, perforation, diarrhoea, flatulence, constipation, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease.	Not known
Renal and urinary disorders	Renal dysfunction, increased blood uric acid levels and renal urate calculi formation.	Not known
Hepatobiliary disorders	Reye's syndrome. (see *Warnings and Precautions*) Elevation in aminotransferase levels.	Not known
Blood and lymphatic system disorders	Prolonged bleeding time. Thrombocytopenia. Ecchymosis	Not known
Metabolism and Nutrition disorders	Sodium and fluid retention.	Not known
Immune system disorders	Hypersensitivity reactions e.g. rhinitis, angioedema, urticaria, bronchospasm, skin reactions and anaphylaxis.	Not known
Ear and labyrinth disorders	Tinnitus, temporary hearing loss.	Not known
Respiratory, thoracic and mediastinal disorders	Asthma. Acetylsalicyclic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions in susceptible individuals.	
Vascular disorders	Hypertension	Not known

Skin and subcutaneous tissue disorders	Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.	Very rare

Caffeine

MedDRA SOC	Adverse Reaction	Frequency
Central Nervous System	Nervousness	Not known
	Dizziness	Not known
Cardiac disorders	Palpitation	Not known
Psychiatric disorders	Insomnia, restlessness, anxiety and irritability, nervousness	Not known
Gastrointestinal disorders	Gastrointestinal disturbances	Not known

When the recommended acetylsalicylic acid-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects.

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 website: www.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 120 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: N02BA51
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

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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,
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8 MARKETING AUTHORISATION NUMBER

PA0678/148/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th January 1983

Date of last renewal: 10th January 2008

10 DATE OF REVISION OF THE TEXT

July 2025