SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Anadin Original

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:

Aspirin BP 325mg/tablet
Caffeine PhEur 15mg/tablet
For excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablet for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains and aches and pains.
For the symptomatic treatment of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Adults, the elderly and young persons aged 16 and over:
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 24 hours.
Do not give to children aged under 16, unless specifically indicted (e.g. Kawasaki's disease).

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

For migraine indication: use of this medicine is not recommended for children and adolescents under 18 years of age.

4.3 Contraindications

- Hypersensitivity to the active ingredients or any of the other constituents.
- Patients in whom asthma, bronchospasm, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs).
- History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Peptic ulceration and those with a history of peptic ulceration;
- A history of haemophilia, concurrent anti-coagulant therapy, hypothrombinaemia or other clotting disorders.
- Renal failure (GFR< 15mL/ min/ 1.73m2)
- Hepatic failure
- A history of gout
- Children under 16 years and
- When breast feeding because of possible risk of Reyes Syndrome.

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.

Acetylsalicylic acid is known to cause sodium and water retention which may exacerbate hypertension, congestive heart failure and renal impairment. Caution should be exercised in patients with uncontrolled hypertension (in whom target blood pressure has not been achieved), impairment of hepatic or renal function (avoid if severe), dehydration or diabetes mellitus.

Haematological and haemorrhagic effects can occur and may be severe. Patients should report any unusual bleeding symptoms to their physician. Doses more than 1 g acetylsalicylic acid daily may precipitate acute haemolytic anaemia in patients with G6PDH deficiency.

Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs and may occur at any time during treatment, with or without warning symptoms or a previous history of serious

GI events. These effects generally have more serious consequences in the elderly (see Interactions).

Do not exceed the stated dose.

If symptoms persist for more than 3 days consult your doctor.

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 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).

Should be used with particular caution in elderly patients who are more prone to adverse events.

The concomitant use of acetylsalicylic acid with other systemic NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive undesirable effects (see Interactions).
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

Other NSAIDs: Concurrent use of other NSAIDs or corticosteroids may increase the likelihood of GI side effects risk of adverse effects.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of acetylsalicylic acid with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. 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.

Loop diuretics (e.g., furosemide): 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.
Anticoagulants: Increased risk of bleeding due to antiplatelet effect.

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.

Methotrexate: Delayed excretion and increased toxicity of methotrexate. In case of concomitant use with acetylsalicylic acid, renal function should be monitored.

Warfarin: Low-dose aspirin (75 to 325 mg daily) increases the risk of bleeding when given with warfarin. High doses of aspirin (4 g daily or more) can also increase prothrombin times in patients taking warfarin. Avoid high-dose aspirin. If low-dose aspirin is indicated, monitor for signs of bleeding. Consider giving gastroprotection (e.g. a proton pump inhibitor) to at-risk patients.

Sulfinpyrazone: The uricosuric effects of aspirin and sulfinpyrazone are mutually antagonistic. Concurrent use for uricosuria should be avoided. Doses of aspirin as low as 700 mg can cause an appreciable fall in uric acid excretion but the effects of a small dose are probably of little practical importance. Sulfinpyrazone can cause gastric bleeding and inhibit platelet aggregation which may be additive with aspirin. (Severity – moderate).

Antacids: Antacids may increase the excretion of acetylsalicylic acid by alkalinization of the urine. The serum salicylate concentrations of patients taking aspirin have been reduced to subtherapeutic levels by aluminium and magnesium hydroxide. Care should be taken to monitor serum salicylate levels if any antacid is started or stopped in patients where the control of salicylate levels is critical. Occasional doses of aspirin for analgesia and aspirin given in doses that produce low salicylate levels do not appear to be affected. (Severity - moderate).

Cilostazol: Concurrent use of multiple antiplatelets would be expected to increase the risk of bleeding. Aspirin very slightly increases the exposure to cilostazol with no clinically relevant effect on bleeding times. Be aware of the increased risk of bleeding. Cilostazol is contraindicated with two or more antiplatelets or anticoagulants (UK). (Severity – moderate).

Mifepristone: Theoretically aspirin and NSAIDs might reduce the efficacy of mifepristone. However, evidence from two studies with naproxen and diclofenac suggests no reduction in mifepristone efficacy. No action needed. (Severity – moderate but theoretical).

Probenecid: The uricosuric effects of aspirin and probenecid are mutually antagonistic. Low dose, enteric-coated aspirin appears not to interact. Regular dosing with substantial amounts of salicylates should be avoided, but small very occasional analgesic doses probably do not matter. Serum salicylate

levels of 5 to 10 mg/100 mL are necessary before this interaction occurs. (Severity – moderate).

Sulphonylureas: Acetylsalicylic acid increases their hypoglycaemic effect, thus some downward readjustment of the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.

Thrombolytic: 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).

Venlafaxine/SSRIs: The bleeding risk associated with antiplatelet drugs such as aspirin might be further increased by the concurrent use of an SNRI/SSRI. Advise patients to report bleeding. Consider gastroprotection (such as a proton pump inhibitor) in those at high risk of gastrointestinal bleeding (e.g. history of gastrointestinal bleeding, the elderly). (Severity – severe).

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.

Co-administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal haemorrhage.

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

4.6 Fertility, Pregnancy and lactation

Acetylsalicylic acid

Fertility

There is some evidence that medicinal products that 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 are 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.

Pregnancy

Not recommended for use during pregnancy. Acetylsalicylic acid should be avoided in the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the fetus in the view of the treating physician. Acetylsalicylic acid is contraindicated during the third trimester of pregnancy

as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension (see Contraindications) and a risk of foetal renal impairment with subsequent oligohydramnios. The onset of labour may be delayed, and its duration increased with an increased risk of bleeding tendency in both the mother and child. If the expected benefit to the mother is greater than the possible risk to the foetus, the lowest effective dose and the shortest duration of treatment should be considered.

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.

Caffeine

Pregnancy

MedDRA SOC	**Adverse Reaction**	**Frequency**

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

Lactation

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

Gastrointestinal disorders	Nausea, vomiting, dyspepsia. Gastrointestinal ulceration, gastrointestinal haemorrhage and gastritis.	Not known
Renal and urinary disorders	Renal dysfunction, increased blood uric acid levels.	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

Adverse events are more likely to occur with increasing dose and duration of use.

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 reactions from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labeled dose and considered attributable are tabulated below by MedDRA System Organ Class. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is not known but likely to be rare or very rare (<1/1000).

Acetylsalicylic acid

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, agitation, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions. Cardiac Symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include vomiting, abdominal or stomach pains. Other symptoms of overdosage, associated with the caffeine component, include diuresis and facial flushing. For clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

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

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.

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

Non-clinical safety data on acetylsalicylic acid and caffeine have not revealed findings which are of relevance to the recommended dosage and use of the product, and which are not already addressed in the clinical data section (See Pregnancy and Lactation).Oral administration of caffeine to rats during the period of organogenesis at a dose that was 2.7 fold greater than the clinical dose was reported to cause a decrease in foetal weight and foetal malformations consisting of club foot, ectrodactyly, cleft palate, and retarded ossification. Similar effects, consisting of significant increases in foetal resorptions and foetal malformations that included cleft palate and digital defects, were reported following intraperitoneal administration of caffeine to mice on days 7 through 14 of gestation at a dose that was 3.4 -fold greater than the clinical dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Quinine Sulfate Ph Eur
Maize Starch Ph Eur
Microcrystalline Cellulose Ph Eur
Hydroxypropyl Methylcellulose (Methocel E5) Ph Eur
Hydroxypropyl Methylcellulose (Methocel E15) Ph Eur
Polyethylene Glycol (Carbowax 3350) USNF
Calcium Stearate USNF

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months:

Cartons containing PVC/ aluminium glassine paper blister strip 4, 6, 8, 12, 16 tablets.

24 Months:

Paper/Polyethylene strip 4, 8
Aluminium containers with approved polyethylene CRC Cap 16
Paper/Polyethylene laminated strip packs 4, 8

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Cartons containing PVC/ aluminium glassine paper blister strip 4, 6, 8, 12, 16 tablets.

Paper/Polyethylene strip 4, 8
Aluminium containers with approved polyethylene CRC Cap 16
Paper/Polyethylene laminated strip packs 4, 8

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Haleon UK Trading Limited,
The Heights,
Weybridge,
Surrey,
KT13 0NY,
U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0203

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 August 1993

10 DATE OF REVISION OF THE TEXT

12/06/2024