Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anadin Extra Film-coated Tablets
Aspirin 300mg
Paracetamol 200mg
Caffeine 45mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:	mg/tablet
Acetylsalicylic Acid	300.0 mg
Paracetamol	200.0 mg
Caffeine	45.0 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet (tablet).

Product imported from UK
A Capsule shaped white tablet with a break bar on one side and with ‘A‘and ‘E’ debossed on the other side.
The scoreline is to allow breaking for ease of swallowing.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of pain of:

- Headache.
- Neuralgia.
- Myalgia.
- Rheumatism.
- Toothache.
- Dysmenorrhoea.
- Symptoms of the common cold or influenza.

4.2 Posology and method of administration

Adults and Adolescents over 16 years:

1 - 2 tablets every 4 hours with a maximum of 6 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.

The Elderly:

Dosage is as above.

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.

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

4.3 Contraindications

- Hypersensitivity to the active ingredients or any other constituents. Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to Anadin Extra, aspirin or other non-steroidal anti-inflammatory drugs or any of the other constituents.
- Bleeding disorders, concurrent anti-coagulant therapy.
- Children, adolescents under 16 years and when breast feeding because of possible risk of Reye's Syndrome (see section 4.6).
- 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).
- Patients with severe heart failure.

4.4 Special warnings and precautions for use

- The use of Anadin Extra 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 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 advised in patients receiving concomitant medication 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 Extra Tablets, 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).
- Patients with a history of inflammatory bowel disease, coagulation disorders, asthma or allergic disease 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. Reyes'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 the patient is taking any other medications or is 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 reaction, 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 Extra 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

Aspirin

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.**

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-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.

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.

Paracetamol

- Cholestyramine:	The absorption of paracetamol is reduced by cholestyramine. Therefore cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and Domperidone:	The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin:	Potentiation of warfarin with continual high dosage of paracetamol.
- Chloramphenicol:	Increased plasma concentration of chloramphenicol.

4.6 Fertility, pregnancy and lactation

As with all other drugs, aspirin and paracetamol should be used during pregnancy only after strict risk benefit evaluation. There is clinical and epidemiological evidence of safety of aspirin in pregnancy, but it may prolong labour and contribute to maternal and neonatal bleeding, may cause premature closure of the ductus arteriosus and so should not be used in the last trimester of pregnancy.

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.

There is epidemiological evidence of safety of paracetamol in human pregnancy.

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

The most common observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation of GI bleeding, sometiems fatal in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, excerbation 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. Bronchospasm, rhinitis and skin reactions in hypersensitive patients. Aspirin may induce gastro-intestinal haemorrhage, occasionally major with signs such as haematemesis and melena. It may precipitate gout in susceptible individuals. Possible risk of Reye’s Syndrome in children under 16 years. Isolated reports of thrombocytopenic purpura, methaemoglobinaemia and agranulocytosis have occurred after paracetamol use.

In isolated cases, following prolonged administration or overdose, chronic hepatic necrosis, acute pancreatitis and nephrotoxicity have been associated with NSAID use. Such side effects are not expected when the product is used as intended.

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

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

High doses of caffeine can cause tremor and palpitations.

4.9 Overdose

Aspirin:

Severe intoxication from heavy overdosage is shown by hyperventilation, fever, restlessness, ketosis, respiratory alkalosis, metabolic acidosis and convulsions. Gastrointestinal haemorrhage is frequent in overdose.

Paracetamol:

Immediate medical advice should be sought in the event of overdosage because of the risk of irreversible liver damage.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion and this may be manifested in increasing prothrombin time, which is a reliable indicator of deteriorating liver function. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is likely in adults who have taken 10g or more of paracetamol but has also occurred at doses lower than this. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Treatment

Aspirin:

A worthwhile recovery of salicylates can be achieved up to 24 hours after ingestion. Treatment must be in hospital where plasma salicylate pH and electrolytes can be measured. Fluid losses are replaced and forced alkaline diuresis is considered when the plasma salicylate concentration is greater than 500mg/litre (3.6 mmol/litre) in adults or 300mg/litre (2.2 mmol/litre) in children.

Paracetamol:

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Any patient who has ingested around 7.5g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Intravenous N-Acetylcysteine or oral methionine protects the liver if administered within 8 to 12 hours of ingesting the overdose. N-Acetylcysteine is effective up to and possibly beyond 24 hours, but expert advice is essential. General supportive measures must be available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02BA51
Pharmacotherapeutic group: Other analgesics and antipyretics.

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 (Non-steroidal)

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.

PARACETAMOL

Mechanism of action/effect

Analgesic

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominately by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulations.

Antipyretic

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

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 that 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 enhanced 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.

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

ASPIRIN

Absorption and Fate

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

PARACETAMOL

Absorption and Fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less then 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

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 pre-systemic 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 formylamion, 3-methyluracil (AMFU).

5.3 Preclinical safety data

The active ingredients in Anadin Extra Tablets have a well established safety record. This combination of ingredients has been marketed for a number of years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Microcrystalline Cellulose (E460)
Hydrogenated Vegetable Oil
Hydroxypropyl Methylcellulose (E464)
Polyethylene glycol
Pregelatinised Starch
Povidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin

6.4 Special precautions for storage

Do not store above 25°C
Store in the original package (to protect from moisture).

6.5 Nature and contents of container

Blister packs containing 16 tablets in an overlabelled carton

6.6 Special precautions for disposal and other handling

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Ltd
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/76/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010

10 DATE OF REVISION OF THE TEXT