Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Excedrin 250 mg/ 250 mg/ 65 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 250 mg acetylsalicylic acid (aspirin), 250 mg paracetamol and 65 mg caffeine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong-shaped, film-coated tablet with the letter "E" debossed on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Excedrin is indicated in adults for the acute treatment of headache and of migraine attacks with or without aura.

4.2 Posology and method of administration

Posology

Adults (18 years and older)

Forheadache:

The usual recommended dosage is 1 tablet; an additional tablet can be taken, with 4 to 6 hours between doses. In case of more intense pain, it is possible to take 2 tablets. If needed, additional 2 tablets can be taken, with 4 to 6 hours between doses.
Excedrin is intended for episodic use, up to 4 days for headache.

Formigraine:

Take 2 tablets when symptoms appear. If needed additional 2 tablets can be taken, with 4 to 6 hours between doses.
Excedrin is intended for episodic use, up to 3 days for migraine.
For both headache and migraine, intake must be limited to 6 tablets in 24 hours. The medicinal product must not be used for a longer period or at a higher dosage without first consulting a doctor. (see section 4.4).
Drink a full glass of water with each dose. Children and adolescents (under 18 years ofage)

Safety and efficacy of Excedrin in children and adolescents have not been evaluated. Use of Excedrin in children and adolescents is therefore not recommended (see section 4.4).

Elderly
Based on general medical considerations, caution should be exercised in the elderly, particularly in elderly patients with low body weight.

Hepatic and renalimpairment
The effect of hepatic or renal disease on the pharmacokinetics of Excedrin has not been evaluated. Due to the mechanism of action of acetylsalicylic acid and paracetamol, this could enhance the renal or hepatic impairment. Thus, Excedrin is contraindicated in patients with severe hepatic or severe renal impairment and failure (e.g. GFR <30mL/min/1.73m^2) (see

section 4.3), and should be used with caution in patients with mild to moderate hepatic or mild to moderate renal impairment (GFR >30mL/min/1.73^2) (see section 4.4).

4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid, paracetamol, caffeine or to any of the excipients listed in section 6.1. Patients in whom attacks of asthma, bronchospasm, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs such as diclofenac or ibuprofen.
- Active gastric or intestinal ulcer, gastrointestinal bleeding or perforation and in patients with a history of peptic ulceration.
- Haemophilia or other haemorrhagic disorders
- Severe hepatic failure or severe renal impairment or failure (GFR <30mL/min/1.73m2)
- Severe cardiac failure
- Intake of more than 15 mg methotrexate per week (see section 4.5)
- Last trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

General:

- Excedrin should not be taken together with other products containing acetylsalicylic acid or paracetamol.
- As with other acute migraine therapies, before treating a suspected migraine in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.
- Patients who experience vomiting with > 20% of their migraine attacks or who require bedrest with >50% of their migraine attacks should not use Excedrin.
- If the patient gets no migraine relief from the first 2-tablet dose of Excedrin, the patient should seek the advice of a physician.
- Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have chronic headaches (15 days or more per month) with concurrent overuse of headache medications for more than 3 months. Therefore, this product should not be used on more than 10 days per month for more than 3 months.
- Caution should be exercised in patients at risk of being dehydrated (e.g. by sickness, diarrhoea, or before or after major surgery).
- Excedrin may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Due to the presence of acetylsalicylic acid:

- 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 section 4.5).
- Excedrin should be used with caution in patients suffering from gout, impaired renal or hepatic function, dehydration, uncontrolled hypertension, and diabetes mellitus.
- Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.
- Acetylsalicylic acid is known to cause sodium and water retention which may exacerbate hypertension, congestive heart failure and renal impairment.
- Excedrin should be used with caution in patients suffering from severe glucose-6- phosphate dehydrogenase (G6PD) deficiency, as acetylsalicylic acid may induce hemolysis or hemolytic anemia. Factors that may increase the risk of hemolysis are e.g. high dosage, fever or acute infections.
- Excedrin may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions) because of the inhibitory effect on platelet aggregation of acetylsalicylic acid which persists for about 4 to 8 days after administration.
- Acetylsalicylic acid decreases platelet adhesiveness and increases bleeding time. Hematological and hemorrhagic effects can occur and may be severe. Patients should report any unusual bleeding symptoms to their physician.

- Excedrin should not be taken together with anticoagulant or other medicines that inhibit platelet aggregation without a doctor's supervision (see section 4.5). Patients with defects of haemostasis should be carefully monitored. Caution should be exercised in case of metrorrhagia or menorrhagia.
- Excedrin must be withdrawn immediately if gastrointestinal (GI) bleeding or ulceration occurs in patients receiving this medicinal product. 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. They generally have more serious consequences in the elderly. The risk of GI bleeding could be enhanced by alcohol, corticosteroids and NSAIDs (see section 4.5).
- Excedrin may precipitate bronchospasm and induce asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma) or other hypersensitivity reactions. Risk factors are present bronchial asthma, seasonal allergic rhinitis, nasal polyps, chronic obstructive pulmonary disease or chronic infection of the respiratory tract (especially if linked to allergic rhinitis-like symptoms). This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances. Special precaution is recommended in such patients (readiness for emergency).
- Excedrin should not be given to children and adolescents aged under 18 years unless specifically indicated because there is a possible association between acetylsalicylic acid and Reye's syndrome when given to children and adolescents. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal.
- Acetylsalicylic acid can interfere with thyroid function tests due to falsely low concentrations of levothyroxine (T4) or tri-iodothyronine (T3) (see section 4.5)

Due to the presence of paracetamol:

- Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Underlying liver disease increases the risk of paracetamol- related liver damage.
- The overall benefit-risk should be considered in patients diagnosed with liver or kidney impairment before use.
- Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol or have sepsis.
- In patients with glutathione depleted states, the use of paracetamol may increase the risk of metabolic acidosis.
- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicinal products or medicinal products that induce liver microsomal enzymes (e.g. rifampicin, isoniazide, chloramphenicol, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine).
- Patients should be warned not to take other products containing paracetamol concurrently due to the risk of severe liver damage in case of overdose (see section 4.9).
- Alcoholic beverages should be avoided while taking this medicine because alcohol use in combination with paracetamol may cause liver damage (see section 4.5).
- Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt
- discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Due to the presence of caffeine:

- Excedrin should be given with care to patients with gout, hyperthyroidism and arrhythmia.

- The patient should limit the use of caffeine containing products when taking Excedrin, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heart beat.

Information concerning excipients:

- Excedrin contains 0.03 mg benzoic acid per tablet. Benzoic acid may increase jaundice in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid, paracetamol and caffeine combination medicines should not be used together with other non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid and cylcooxygenase-2 specific inhibitors as these may increase the risk of adverse effects.
Medicinal product interactions with other substances that might be caused by each individual ingredient are well-known and there is no indication that those might change through combined use. There are no safety-relevant interactions between acetylsalicylic acid and paracetamol.

Table 4-1 Acetylsalicylic acid(ASA)

Combination of Acetylsalicylic acid with:	*Possible outcome:*
Other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	There is an increased risk of GI ulcers and haemorrhages due to synergic effects. If concurrent use is necessary, where appropriate, the use of gastroprotection may be considered for prophylaxis of NSAID-induced GI damage. Thus, concomitant use is not recommended (see section 4.4).
Corticosteroids	There is an increased risk of GI ulceration or bleeding due to synergic effects. It may be advisable to consider the use of gastroprotection in patients taking ASA and corticosteroids, especially if they are elderly. Thus, concomitant use is not recommended (see section 4.4).
Oral anticoagulants (e.g. coumarin derivatives)	ASA can increase the anticoagulant effect. Clinical and laboratory monitoring of the bleeding time and prothrombin time should be performed. Concomitant use is therefore not recommended (see section 4.4).
Thrombolytics	There is an increased risk of bleeding. Particularly, treatment with ASA should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended (see section 4.4).
Heparin & Platelet aggregation inhibitors (ticlopidine, clopidogrel, cilostazol)	There is an increased risk of bleeding. Clinical and laboratory monitoring of the bleeding time should be performed. Concomitant use is therefore not recommended (see section 4.4).
Selective Serotonin Reuptake Inhibitors (SSRIs)	They could affect coagulation or platelet function when concomitantly taken with ASA, leading to increased occurrence of bleeding in general, and in particular GI bleeding. Therefore, concomitant use should be avoided.
Phenytoin	ASA increases its serum levels; serum phenytoin should be well monitored.
Valproate	ASA inhibits its metabolism and hence could increase its toxicity; valproate levels should be well monitored.
Aldosterone antagonists (spironolactone, canrenoate)	ASA may reduce their activity due to inhibition of urinary sodium excretion; blood pressure should be well monitored.
Loop diuretics (e.g. furosemide)	ASA 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 ASA, it is necessary to ensure adequate hydration of the patient and to monitor the kidney function and blood pressure, particularly when starting diuretic treatment.
Antihypertensives (ACE- inhibitors, angiotensin II receptor	ASA may reduce their activity due to competition and

antagonists, calcium-channel blockers)	inhibition of urinary prostaglandins. This combination could lead to acute kidney failure in elderly or dehydrated patients. It is recommended that blood pressure and renal function should be well monitored when starting treatment and the patient should be regularly hydrated. In case of association with verapamil the bleeding time should be also monitored.
Uricosurics (e.g. probenecid, sulfinpyrazone)	ASA may reduce their activity due to inhibition of tubular resorption, leading to high plasma levels of ASA.
Methotrexate ≤ 15 mg/week	ASA, like all NSAIDs, reduces the tubular secretion of methotrexate, increasing its plasma concentrations and thereby also its toxicity. The concomitant use of NSAIDs is therefore not recommended in patients treated with high doses of methotrexate (see section 4.3). The risk of interactions between methotrexate and NSAIDs must also be considered for patients who take low doses of methotrexate, especially those with altered kidney function. If combined treatment is necessary, the complete blood count, liver and renal functions should be monitored, especially during the first days of treatment.
Sulphonylureas and insulin	ASA 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.
Alcohol	There is an increased risk of GI bleeding; this combination should be avoided.

Table 4-2 Paracetamol

Combination of paracetamol with:	*Possible outcome:*
Liver enzyme inducers or potentially hepatotoxic substances (eg., alcohol, rifampicin, isoniazide, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine)	Increased toxicity of paracetamol that could lead to liver damage even with otherwise harmless doses of paracetamol; therefore, liver function should be monitored (see section 4.4). Concomitant use is not recommended.
Chloramphenicol	Paracetamol may increase the risk of elevated plasma concentrations of chloramphenicol. Concomitant use is not recommended.
Zidovudine	Paracetamol could increase the tendency to develop neutropenia; therefore, the hematological blood monitoring should be performed. Concomitant use is not recommended unless monitored by a doctor.
Probenecid	It reduces paracetamol clearance, thus paracetamol doses should be decreased when combined with these agents. Concomitant use is not recommended.
Oral anticoagulants	The repeated use of paracetamol for more than one week increases anticoagulant effects. Sporadic doses of paracetamol do not have a significant effect.
Propantheline or other agents that lead to slowing of gastric emptying	These agents delay paracetamol absorption; rapid pain relief may be delayed and reduced.
Metoclopramide or other agents that lead to acceleration of gastric emptying	These active substances accelerate the paracetamol absorption with increase of the effectiveness and onset of analgesia.
Cholestyramin	It reduces paracetamol absorption; therefore cholestyramin should not be given within 1 hour of paracetamol if maximal analgesia is to be achieved.
Flucloxacillin	Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake

	has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

Table 4-3 Caffeine

Combination of caffeine with:	*Possible outcome:*
Hypnotic agents (eg., benzodiazepines, barbiturates, antihistamines, etc)	Concomitant use can reduce the hypnotic effect, or antagonize the anticonvulsive effects of barbiturates. Concomitant use is therefore not recommended. If needed, the combination may possibly be more useful in the morning.
Lithium	Caffeine withdrawal increases serum lithium since renal clearance of lithium can be increased by caffeine, therefore when caffeine is withdrawn, it may be necessary to reduce the dose of lithium. Concomitant use is therefore not recommended.
Disulfiram	Alcoholic patients who are recovering using treatment with disulfiram must be warned to avoid the use of caffeine in order to avoid the risk of alcohol abstinence syndrome worsening due to caffeine-induced cardiovascular and cerebral excitation.
Substances of the ephedrine type	Their combination could have an increased dependency potential. Concomitant use is therefore not recommended.
Sympathomimetics or levothyroxine	Their combination could have an enhanced tachycardic effect due to synergic effects. Concomitant use is therefore not recommended.
Theophylline	Concomitant use could reduce the excretion of theophylline.
Antibacterials of the quinolone type (ciprofloxacin, enoxacin, and pipemidic acid), terbinafine, cimetidine, fluvoxamine and oral contraceptives	Increased caffeine half-life due to inhibition of the hepatic cytochrome P - 450 pathway; therefore, patients with hepatic disorders, cardiac arrhythmias or latent epilepsy should avoid taking caffeine.
Nicotine, phenytoin and phenylpropanolamine	They decrease the elimination half-life of caffeine.
Clozapine	Caffeine increases the serum levels of clozapine due to the probable interaction through both pharmacokinetic and pharmacodynamic mechanisms. Clozapine serum levels should be monitored. Concomitant use is therefore not recommended.

Interaction with laboratory testing

- High doses of ASA can affect the results of several clinical-chemical laboratory tests.
- Paracetamol intake can affect the results of uric acid when using the phosphotungstic acid method and for glycaemia when using the glucose oxidase/peroxidase method.

Caffeine can inverse the effects of dipyridamole and adenosine on myocardial blood flow, thereby interfering with the results of myocardial imaging tests. It is recommended that the ingestion of caffeine be suspended at least 24 hours prior to the test.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not recommended for use during pregnancy. This medicine is contraindicated during the third trimester of pregnancy (see section 4.3).

There are no adequate data available from the use of Excedrin in pregnant women. Animal studies have not been performed with acetylsalicylic acid, paracetamol and caffeine in combination (see section 5.3).

Acetylsalicylic acid

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, acetylsalicylic acid 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, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid 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 acetylsalicylic acid for several days from gestational week 20 onward. Acetylsalicylic acid 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, acetylsalicylic acid is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Paracetamol
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Caffeine

There is evidence that the prolonged intake of high amounts of caffeine may lead to spontaneous abortion or premature birth in pregnant women. Non-clinical studies have shown reproductive toxicity at very high doses.

Breast-feeding

Salicylate, paracetamol and caffeine are excreted into breast milk. Due to the content of caffeine, the behaviour of the suckling child may be influenced (excitement, poor sleeping pattern). Due to the salicylate, there may also be a potential for adverse effects on platelet function in the infant (could cause slight bleeding), though none have been reported. Also, there are concerns with the use of ASA in case of potential development of Reye's Syndrome in infants. Therefore, Excedrin is not recommended during breastfeeding.

Fertility

Acetylsalicylic acid

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.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed. If you notice undesirable effects such as dizziness or drowsiness, you should not drive or use machines.Tell your doctor as soon as possible.

4.8 Undesirable effects

Many of the following adverse reactions are clearly dose-dependent and variable from one person to another.
Table 4-4 provides a listing of adverse reactions from 16 single-dose clinical studies on the efficacy and safety of Excedrin in the treatment of migraine, headache or dental pain associated with tooth extraction, involving 4809 Excedrin-treated subjects, and from post- marketing spontaneous reports. The adverse reactions included in the table were those regarded as at least possibly related to the administration of Excedrin and are listed in descending order of frequency within MedDRA System Organ Classification.
For adverse reactions from the spontaneous reporting system, the frequencies cannot be reliably determined and therefore, is not known.
Adverse reactions are listed below by system organ class and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), including isolated reports and not known (cannot be estimated from the available data).

Table 4-4 ***Adverse reactions reported from clinical studies and frompost- marketing spontaneousreports***

System OrganClass	**Frequency**	**PreferredTerm**
Infections and infestations	Rare	Pharyngitis
Blood and lymphatic system disorders	Not known	Prolonged bleeding time, thrombocytopenia, ecchymosis
Immune system disorders	Not Known	Hypersensitivity*, anaphylactic reaction, Stevens Johnson syndrome, toxic epidermal necroysis
Metabolism and nutrition disorders	Rare Not known	Decreased appetite Sodium and fluid retention, high anion gap metabolic acidosis
Psychiatric disorders	Common	Nervousness
	Uncommon	Insomnia
	Rare	Anxiety, euphoric mood, tension
	Not Known	Restlessness
Nervous system disorders	Common	Dizziness
	Uncommon	Tremor, paraesthesia, headache
	Rare	Dysgeusia, disturbance in attention, amnesia, coordination abnormal, hyperaesthesia, sinus headache
	Not Known	Migraine, somnolence
Eye disorders	Rare	Eye pain, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
	Not known	Temporary hearing loss.
Cardiac disorders	Uncommon	Arrhythmia
	Not Known	Palpitations
Vascular disorders	Rare	Flushing, peripheral vascular disorder
	Not Known	Hypotension
Respiratory, thoracic and mediastinal disorders	Rare	Epistaxis, hypoventilation, rhinorrhoea
	Not known	Bronchospasm
	Not Known	Dyspnoea, asthma
Gastrointestinal disorders	Common	Nausea, abdominal discomfort
	Uncommon	Dry mouth, diarrhoea, vomiting
	Rare	Eructation, flatulence, dysphagia, paraesthesia oral, salivary hypersecretion
	Not Known	Abdominal pain upper, dyspepsia, abdominal pain, GI haemorrhage (including upper GI haemorrhage, gastric haemorrhage, gastric ulcer haemorrhage, duodenal ulcer

		haemorrhage, rectal haemorrhage), GI ulcer (including gastric ulcer, duodenal ulcer, large intestinal ulcer, peptic ulcer), gastritis
Hepatobiliary disorders	Not Known	Hepatic failure, hepatic enzyme increased, Reye's syndrome (see section 4.3)
Skin and subcutaneous tissue disorders	Rare	Hyperhidrosis, pruritus, urticaria
	Not Known	Erythema, rash, angioedema, erythema multiforme
Musculoskeletal and connective tissue disorders	Rare	Musculoskeletal stiffness, neck pain, back pain, muscle spasms
Renal and urinary disorders	Not known	Renal dysfunction, increased blood uric acid levels
General disorders and administration site conditions	Uncommon	Fatigue, feeling jittery
	Rare	Asthenia, chest discomfort
	Not Known	Malaise, feeling abnormal

*including rhinitis
Very rare cases of serious skin reactions have been reported.

There is no information available to suggest that the extent and type of adverse events of the individual substances is enhanced or the spectrum broadened when the fixed combination is used as instructed.

Description of selected adverse reactions
High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Increase of the risk of bleeding can persist for 4-8 days after the intake of acetylsalicylic acid. Very rarely severe bleeding (e.g. intracerebral bleeding) especially in patients with untreated hypertension and / or concomitant treatment with anticoagulants. In single cases these can be life threatening.

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

Linked to Acetylsalicylicacid:

Symptoms of mild salicylate intoxication include dizziness, tinnitus, deafness, sweating, warm extremities with bounding pulses, nausea and vomiting, dehydration, headache and confusion. These may occur at plasma concentrations of
150 to 300 micrograms/ml. These symptoms can be controlled by reducing the dose, or interrupting the treatment.
More serious intoxication occurs at concentrations above 300 micrograms/ml. The symptoms of severe overdose include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis, and metabolic acidosis. Depression of the CNS may lead to coma. Cardiovascular collapse and respiratory failure may also occur.
Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.
Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment of severeoverdose

The patient must be transferred to hospital and the Poison Control Center contacted immediately.
When the patient is suspected of ingesting more than 120 mg/kg salicylate within the last hour, repeated doses of activated charcoal are to be given orally.

Plasma concentrations should be measured in patients having ingested more than 120 mg/kg salicylate, although the severity of the poisoning cannot be determined from these alone. Clinical and biochemical features must equally be taken into account.
In plasma concentrations exceeding 500 micrograms/ml (350 micrograms/ml in children under 5 years of age) the intravenous administration of sodium bicarbonate is effective in removing salicylate from the plasma. Forced diuresis should not be used alone since it does not enhance salicylate excretion and may cause pulmonary oedema.
Heamodialysis or haemoperfusion are the methods of choice in cases where the plasma salicylate concentration is more than 700 micrograms/ml, or lower in children and elderly people, or if there is a severe metabolic acidosis.

Linked toParacetamol:

Overdose (>10 g in total in the adult or >150 mg/kg in one intake) can provoke a hepatic cytolysis which can lead to complete and irreversible necrosis (hepatic failure, metabolic acidosis, renal failure) and eventually to coma and possibly death or may require liver transplant. Less often renal tubular necrosis may develop.
Early signs of overdose (very commonly nausea, vomiting, anorexia, pallor, lethargy and sweating) generally settle within first 24 hours.
Abdominal pain may be the first indication of liver damage, which is not usually apparent for the first 24 to 48 hours, and may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.
Patients are considered at high risk when receiving enzyme-inducing medicinal products, such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or with a history of alcohol abuse, or suffering from malnutrition.

Treatment ofoverdose:

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present.
If overdose is confirmed or suspected, seek immediate advice from your Poison Centre and refer patient to nearest Emergency Medical Centre for management and expert treatment. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage.
When the patient is suspected of ingesting more than 150 mg/kg paracetamol within the last hour, repeated doses of activated charcoal are to be given orally. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.

Antidotes

N-acetylcysteine should be administered intravenously or orally as soon as possible after ingestion. It is most effective during the first 8 hours after taking the overdose. The effect of the antidote then diminishes progressively after that. Nevertheless it has been shown that treatment up to and beyond 24 hours after ingestion remains beneficial.
Methionine is most effective within the first 10 hours after ingestion of paracetamol overdose. Hepatic damage is more frequent and severe if treatment with methionine if started more than 10 hours after ingestion.
Oral absorption might be reduced by vomiting or activated charcoal.

Linked toCaffeine:

Common symptoms include epigastric pain, vomiting, anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, tremors and convulsions. For high intake of caffeine, hyperglycemia could also appear. Cardiac Symptoms include tachycardia and cardiac arrhythmia. The symptoms are controlled by reducing or stopping caffeine intake.
For clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics; Salicylic acid and derivatives
ATC code: N02B A51.

Mechanism of action
Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory properties, primarily due to the inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid by irreversible acetylation of cyclooxygenase (COX) enzymes.
Paracetamol has analgesic and antipyretic properties, but unlike acetylsalicylic acid does not inhibit platelet aggregation.
The addition of caffeine augments the antinociceptive effects of acetylsalicylic acid and paracetamol.

Pharmacodynamic Effects
Acetylsalicylic acid
Acetylsalicylic acid is an anti-inflammatory agent, mainly due to inhibition of inflammatory mediators via cyclooxygenase inhibition in peripheral tissues. This suppression of cyclooxygenase pathway in peripheral tissues may lead to its primary side effect of gastric irritation.
Low doses of acetylsalicylic acid affect platelet aggregation by irreversibly inhibiting platelet cyclooxygenase (COX-1). This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. At higher doses (more than 150-300 mg/day), acetylsalicylic acid reversibly inhibits in endothelial cells the cyclooxygenase dependent formation of prostaglandin I2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation, however there is no evidence that aspirin is thrombogenic in man.

Paracetamol
Central mechanisms of action have been proposed for paracetamol and peripheral tissues may be influenced differentially. For protective prostaglandins within the gastrointestinal track, only a slight inhibitory effect of paracetamol has been reported.

Caffeine
Caffeine enhances the analgesic effect of paracetamol and acetylsalicylic acid and shortens the time to onset of analgesic effect.

Migrainestudies

The efficacy of Excedrin tablets in the treatment of acute migraine attacks was confirmed in 3 single-dose, double-blind, placebo-controlled studies and in 2 single-dose, double-blind, placebo and active controlled studies, one versus ibuprofen 400 mg and the other one versus sumatriptan 50 mg. In these studies, single-dose of Excedrin consisted of 2 tablets (500 mg acetylsalicylic acid, 500 mg paracetamol, 130 mg caffeine).
In the three placebo-controlled studies, Excedrin APC was superior to placebo in reducing migraine pain intensity to mild or none 2 hours after dose in the drug–treated patients. It started relieving migraine symptoms, such as migraine pain, within 30 minutes.
In a placebo and active controlled study, Excedrin APC and ibuprofen (2 tablets of ibuprofen 200 mg) were compared in the treatment of migraine. Excedrin APC was shown to deliver significantly greater pain relief than ibuprofen starting at 2 hours post dose and to deliver clinically meaningful pain relief 20 minutes faster.
In another placebo and active controlled pilot study, Excedrin APC was compared with sumatriptan 50 mg and placebo for the early treatment of migraine. In this study Excedrin APC was shown to be significantly more effective than sumatriptan 50 mg at reducing migraine pain intensity throughout the 4-hour treatment period. Sumatriptan 50 mg was shown to be superior to placebo with respect to this variable, but not to a statistically significant degree.
In a separate placebo and active controlled post-marketing study, Excedrin was not shown to be non-inferior to sumatriptan 100 mg. However in the acute treatment of migraine, Excedrin provided pain and symptom relief over 24 hours.
Overall, the efficacy of Excedrin has been demonstrated in the relief of migraine symptoms such as headache, nausea, sensitivity to light and sound, and functional disability.

Headachestudies

The efficacy of Excedrin tablets was studied in 4 independent, multi-center, double-blind, paracetamol 1000 mg and placebo-controlled crossover studies in the treatment of episodic tension-type headache. In all of these studies, Excedrin was shown to be consistently superior to placebo and active comparators (mono-substances) regarding all efficacy measures of pain intensity and relief throughout the observation period.
Another multi-centre, double-blind, tension-type headache clinical trial compared the onset of analgesia between Excedrin, placebo and ibuprofen 400 mg. In this study, Excedrin-treated subjects reported significantly greater pain relief than

placebo-treated subjects from 15 minutes through 4 hours. This finding was evident in both the Pain Relief and Responders endpoints.

5.2 Pharmacokinetic properties

Acetylsalicylicacid

Absorption
Acetylsalicylic acid is completely absorbed from the gastrointestinal (GI) tract after oral administration. Approximately 70% of an acetylsalicylic acid dose reaches the circulation unchanged; the remaining 30% is hydrolyzed to salicylic acid during absorption by esterases in the GI tract, liver or plasma. The salicylate peak plasma concentration is reached in 1-2 hours with single doses. Food reduces the speed but not the extent of absorption.

Distribution
Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS). The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. Acetylsalicylic acid and salicylic acid bind partially to serum proteins and mainly to albumin. The protein binding of salicylate is concentration-dependent, i.e., nonlinear. At low concentrations (< 100 micrograms/milliliter (mcg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 (mcg/mL)), only about 40-70% is bound.
Salicylic acid crosses the placenta and is excreted in breast milk.

Metabolism
Acetylsalicylic acid is hydrolyzed in the plasma to salicylic acid (with a half-life of 15-20 minutes) such that plasma levels of acetylsalicylic acid are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid by conjugation with glycine, salicyl phenolic glucuronide and salicyl acyl glucuronide by conjugation with glucuronic acid, and a number of minor metabolites. Following a single 1 g dose of acetylsalicylic acid, the average half-life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. The half-life of salicylate varies with dosage. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

Elimination
Salicylic acid and its metabolites are excreted through the kidneys. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises from 5 up to 8, greater fraction of the administered dose is eliminated as free salicylic acid and the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

Paracetamol

Absorption:
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion.

Distribution:
Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism:
It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates.
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 overdose and cause liver damage.

Elimination:
Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours.

Caffeine

Absorption:
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.

Distribution:
Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Metabolism:
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).

Elimination:
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.

Combination

In the combination of the three active ingredients, the quantity of each substance is low. Therefore no saturation of the elimination processes with the consequential risks of increased half-life and toxicity.
Pharmacokinetic data for the fixed combination of acetylsalicylic acid, paracetamol and caffeine are in line with the pharmacokinetic profiles established either for each of the substances alone or for the combination of each analgesic with caffeine.
Neither critical drug-drug interactions between acetylsalicylic acid, paracetamol and caffeine nor any increased risk of interactions with other medicinal products through their combined use are known. Findings with respect to pharmacokinetics of Excedrin were as expected, and no interactions between the 3 active substances have been observed.

5.3 Preclinical safety data

Acetylsalicylicacid

Preclinical studies in animals using acetylsalicylic do not show organ toxicity except for effects on gastrointestinal mucosa and, at high dosages, renal damage. Acetylsalicylic acid is neither mutagenic nor carcinogenic. Salicylates have been found to have teratogenic effects at maternally toxic doses in a number of animal species (e.g. cardiac and skeletal malformations, midline defects). There have been reports of implantation disturbance, embryotoxic and fetotoxic effects, and disturbance of learning capacity in the offspring after prenatal exposure.

Paracetamol

Preclinical data reveal no special hazard for humans at therapeutically relevant doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.
Overdose may lead to serious hepatotoxicity.

Caffeine

Caffeine was shown to be devoid of mutagenic and oncogenic risk. In animal studies in different species (rat, mice, rabbit), very high doses of caffeine were associated with an increase in birth defects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hydroxypropyl cellulose low substitution
Cellulose microcrystalline (E 460)
Stearic acid

Film-coating:
Hypromellose (E 464)
Titanium dioxide (E 171)
Propylene glycol
Benzoic Acid (E 210)
Carnauba wax (E 903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Child-resistant white opaque or transparent blisters composed of PVC/PCTFE/PVC with lacquered aluminium foil laminate backing.
White opaque or transparent blisters composed of PVC/PCTFE/PVC with lacquered aluminum foil non-laminate backing.
White opaque or transparent blisters composed of PVC/PCTFE/PVC with a child resistant aluminium foil/ polyethylene terephthalate (PET) bilayer backing.
Pack sizes: 10, 16, 20, 30 and 32 film-coated tablets
Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Haleon Ireland Limited
Clocherane
Youghal Road
Dungarvan
X35 Y983
Co. Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/122/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 10th February 2014

10 DATE OF REVISION OF THE TEXT

July 2025