Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Excedrin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One caplets contains 250 mg acetylsalicylic acid, 250 mg paracetamol and 65 mg caffeine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Caplets.
White, oblong-shaped, caplet with the letter "E" debossed on one face.

4 Clinical particulars

4.1 Therapeutic indications

For temporary relief of the pain of headache, mild to moderate pain associated with migraine headache, pain of menstrual discomfort and pain accompanied by fever.

4.2 Posology and method of administration

Posology

For headache, pain of menstrual discomfort and pain accompanied by fever:
Adults and Adolescents above 12 years: The usual recommended dosage is 2 caplets every 6 hours.
Pain relief may be felt within 15 minutes of administration the dose.

For migraine headache:
Adults- 2 caplets. If Excedrin is taken for migraine headache, and there is no improvement or there is an exacerbation after the first dose, reconsider the treatment.
Do not use Excedrin for Migraine headache more than 24 hours

Intake should be limited for 8 caplets in 24 hours.
Intake period should be limited for up to 5 days for pain relief and up to 3 days for pain accompanied by fever.

Drink a full glass of water with each dose.
Do not score or crush the capsule.
Do not lie down for 15-30 minutes after administration the capsule.

Children and adolescents
Excedrin is not indicated for children and adolescents under 12 years old.

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

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, 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 inpatients with

a history of peptic ulceration.
• Haemophilia or other haemorrhagic disorders
• Severe hepatic or renal failure
• 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 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-caplet 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. bysickness, 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:
• Excedrin should be used with caution in patients suffering from gout, impaired renal or hepatic function, dehydration, uncontrolled hypertension, and diabetes mellitus.
• 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 days after administration.
• 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 section4.5).

Due to the presence of paracetamol:
• Excedrin should be given with care to patients with impaired renal or hepatic function or alcohol dependence.
• 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 with history of alcohol abuse are at special risk of hepatic damage (see section 4.5).
• 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). Paracetamol should be given with caution to patients with alcohol dependence

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.

4.5 Interaction with other medicinal products and other forms of interaction
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 wellmonitored.
Aldosterone antagonists (spironolactone, canrenoate)	ASA may reduce their activity due to inhibition of urinary sodium excretion; blood pressure should be wellmonitored.
Loop diuretics (e.g. furosemide)	ASA may reduce their activity due to competition and inhibition of urinary prostaglandins. NSAIDs can cause acute kidney failure, especiallyin 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 antagonists, calcium-channel blockers)	ASA may reduce their activity due to competition and 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 andthe 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 ofmethotrexate, 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 beconsidered for patients who take low doses of methotrexate, especially thosewith 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 shouldbe 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.

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

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

Due to the presence of acetylsalicylic acid in Excedrin, its use is contraindicated in the 3rd trimester of pregnancy (see section 4.3), and caution should be exercised when used in the first 2 terms of pregnancy.

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. 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may have the following effects:

On the foetus:

- cardiopulmonary toxicity (with premature closure of the *ductus arteriosus* and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with *oligo-hydroamniosis*; On the mother and the neonate:
- at the end of pregnancy, 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.

Rarely, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after 20 weeks gestation in pregnancy may cause fetal renal dysfunction leading to oligohydramnios.
These effects are seen after days to weeks of treatment. Although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.
The use of NSAIDs after week 20 of gestation should be restricted. If the benefit of NSAID treatment is considered greater than the risk, limit use to the lowest effective dose and shortest duration possible.
Consider ultrasound monitoring of amniotic fluid if NSAID treatment of this medicine at the full treatment dosage extends beyond five days. Discontinue the NSAID if oligohydramnios occurs.

Paracetamol

Epidemiological studies indicate that under normal therapeutically conditions paracetamol can be used during pregnancy. Nevertheless, it should be used only after a careful benefit-risk assessment has been done.

Caffeine

Pregnant women are advised to limit their intake of caffeine to a minimum as the available data on the effect of caffeine on the human fetus suggests a potential risk.

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 from post- marketing spontaneous reports***

System Organ Class	Frequency	Preferred Term
Infections and infestations	Rare	Pharyngitis
Immune system disorders	Not Known	Hypersensitivity, anaphylactic reaction, Stevens Johnson syndrome*, toxic epidermal necroysis*
Metabolism and nutrition disorders	Rare	Decreased appetite
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
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	Dyspnoea, asthma
Gastrointestinal disorders	Common	Nausea, abdominal discomfort
	Uncommon	Dry mouth, diarrhoea, vomiting
	Rare	Eructation, flatulence, dysphagia, paraesthesiaoral, salivaryhypersecretion
	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, largeintestinal ulcer, peptic ulcer)
Hepatobiliary disorders	Not Known	Hepatic failure, hepatic enzymeincreased
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
General disorders and administration site conditions	Uncommon	Fatigue, feeling jittery
	Rare	Asthenia, chest discomfort
	Not Known	Malaise, feeling abnormal

*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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Linked to Acetylsalicylic acid:

Symptoms of mild salicylate intoxication include dizziness, tinnitus, deafness, sweating, nausea and vomiting, 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.

Treatment of severe overdose

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.

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 to Paracetamol:

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. 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 of overdose:

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 to Caffeine:
Common symptoms include anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics; Salicylic acid and derivatives
ATC code: N02B A51.
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.
Migraine studies
The efficacy of Excedrin caplets 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.
Headache studies
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

Acetylsalicylic acid

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

Paracetamol

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 than 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 overdose and cause liver damage.

Caffeine

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 inadults.

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).

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

Acetylsalicylic acid

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.

Acetaminophen

Preclinical data reveal no special hazard for humans at therapeutically relevant doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, or toxicity to reproduction. Overdose may lead to serious hepatotoxicity.

Caffeine

Preclinical data reveal no special hazard for humans based on genotoxicity, carcinogenicity, and reproductive toxicity studies. At high maternally toxic dose level, caffeine has also shown teratogenic effects in animal studies.

There are no preclinical data of relevance to the prescriber additional to that already included in other relevant sections of the SPC. Refer to sections 4.3 and 4.6 for information on use during pregnancy and lactation in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caplet core: Cellulose microcrystalline, Hydroxypropyl cellulose low substitution, Stearic acid
Film-coating: Hypromellose, Titanium dioxide, Propylene glycol, Carnauba wax, Benzoic Acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister pack composed of PVC/PCTFE/PVC with lacquered aluminium foil laminate backing.

Pack sizes: 8,10,16,20,30,32 and 50 caplets.
Not all pack types and sizes may be marketed.

6.6 6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GSK Consumer Healthcare Israel Ltd.
25 Basel St., Petach-Tikva, 4951038, Israel

8 MARKETING AUTHORISATION NUMBER(S)

141-82-31782

9 DATE OF REVISION OF THE TEXT

The format pf this leaflet was determined by ministry of health and its content was updated according to the guidelines of the ministry of health in November 2021.