# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Extra Power Pain Control Caplets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| | |
|---|---|
| Aspirin | 300 mg |
| Paracetamol | 200 mg |
| Caffeine | 45 mg |

For excipients, see 6.1

## 3 PHARMACEUTICAL FORM

Coated tablets.
White, coated, capsule-shaped tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

For oral administration. Swallow whole with water. Do not chew.

Adults, the elderly and children over 16 years of age:
1-2 caplets every 4-6 hours. Maximum of 8 caplets in any 24 hour period.

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

The dose should not be repeated more frequently than every 4 hours.
Do not take for more than 3 days without consulting a doctor.

Gastro-intestinal irritation may be reduced by taking aspirin with or immediately after food.

## 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

**Aspirin**

- Hypersensitivity to aspirin, or any of the excipients (see section 6.1). In patients with a history of hypersensitivity to aspirin (or any of the excipients) or any other NSAIDs and in patients in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or other NSAIDs.
- Use in children under 16 years of age except under the supervision of a doctor (see section 4.4 – aspirin and Reye's syndrome).
- Patients with haemophilia, other coagulopathies or concurrent anticoagulant therapy.
- Gout
- Doses > 100mg/day during the third trimester of pregnancy.

**Caffeine**

Hypersensitivity to caffeine.

Patients with active peptic ulcerations or a history of peptic ulceration.

## 4.4 Special warnings and precautions for use

Paracetamol
Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease. Paracetamol should be given with care to patients with alcohol dependence.
Paracetamol is well tolerated by the majority of people with asthma. However a small percentage of aspirin sensitive asthmatics are also sensitive to paracetamol. The likelihood of a reaction to paracetamol increases with a patient's level of sensitivity to aspirin (see also 4.8 Undesirable effects).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with intravenous busulfan (see section 4.5 Interactions).

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 and 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.

Caffeine

Care is advised in the administration of caffeine to patients with cardiac disease.

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

Aspirin

Caution should be exercised in patients with asthma, allergic disease, , impairment of hepatic or renal function (avoid if severe), impaired cardiac function, uncontrolled hypertension dehydration, dyspepsia and in patients with nasal polyps or a history of nasal polyps.

Aspirin should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked.

The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding.

Care should be taken giving aspirin to patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur.

Aspirin may interfere with insulin and glucagon in diabetes.

Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation, and therefore it should be discontinued several days before scheduled surgical procedures.

Renal, hepatic and haematological status should be monitored during prolonged and high dose aspirin therapy.

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.

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

**General Points**

- Do not exceed the stated dose.
- If symptoms persist consult a doctor. Do not take for more than 3 days without consulting your doctor.
- If you are receiving a course of medicinal treatment, consult your doctor.
- Do not give to children under 16 years of age except on advice from a doctor.
- Keep all medicines out of the reach and sight of children.
- Do not take any other paracetamol-containing products whilst taking this product.

**Special Labelling requirements**

*Label:*

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Contains paracetamol.

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Do not give to children aged under 16 years, unless on the advice of a doctor.

Leaflet:

Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

There is a possible association between aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which can be fatal. For this reason aspirin should not be given to children aged under 16 years, unless on the advice of a doctor

## 4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

Alcohol: Paracetamol should be given with care to patients with alcohol dependence - (see section 4.4)

Analgesics: Diflunisal increases blood concentrations of paracetamol.

Anion-exchange resins: absorption reduced by colestyramine; administration should be separated by at least one hour.

Antibacterials: Isoniazid may increase the risk of hepatotoxicity with therapeutic doses.

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)

Anticoagulants: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding, occasional doses have no significant effect

Antiepileptics: Carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol and increase the risk of hepatotoxicity.

Cytotoxic drugs: Paracetamol possibly inhibits metabolism of intravenous busulfan (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol).

Motility stimulants: The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.

Oral contraceptives: Paracetamol is cleared from the body more quickly in women taking oral contraceptives and the analgesic effects may be reduced.

Uricosurics: Probenecid can reduce the loss of paracetamol from the body.

Caffeine

Antibacterials: Some quinolone antibiotics, including enoxacin, pipemidic acid and ciprofloxacin can reduce the clearance of caffeine and prolong its plasma half-life.

Antidepressants: Fluvoxamine can reduce the clearance of caffeine and increase its stimulant and side effects.

Antiepileptics: Phenytoin may increase the clearance of caffeine.

Antipsychotics: Caffeine may increase serum clozapine levels.

Benzodiazepines: Caffeine can reduce the sedative effects of diazepam.

Disulfiram: may reduce the clearance of caffeine.

Diuretics: Concomitant use of xanthines with diuretics may increase the risk of hypokalaemia.

Ephedrine/ephedra alkaloids in dietary supplements (Ma Huang): Concomitant use may raise blood pressure; hypertension, tachycardia, subarachnoid haemorrhage, cardiac arrest and neurosis have been reported.

Lithium: Caffeine may increase the clearance of lithium.

Mexiletine: may reduce the clearance of caffeine.

Oestrogens and progestogens: Oral contraceptives or oestrogen replacement therapy may reduce the clearance of caffeine.

Phenylpropanolamine: concomitant administration may increase blood pressure, resulting in hypertensive crises in a few susceptible individuals. Manic psychosis has occurred. Phenylpropanolamine can increase serum caffeine levels.

Theophylline: concomitant administration can increase plasma theophylline and plasma caffeine levels.

Aspirin

Alcohol: Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol

Anaesthetics: Aspirin may potentiate the effects of thiopental anaesthesia.

Antacids and adsorbents: The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption.

Anti-coagulants: Aspirin may enhance the effects of anti-coagulants (e.g. increased risk of bleeding with concomitant heparin; increased risk of major bleeding [cerebral/intracranial haemorrhage] with concomitant streptokinase); concurrent use is contraindicated (see Section 4.3).

Anti-epileptics: May enhance the effects of phenytoin and sodium valproate. Increased risk of bleeding when aspirin and sodium valproate or valproic acid used concomitantly.

Antimetabolites: The activity of methotrexate may be markedly enhanced by aspirin and its toxicity increased.

ACE Inhibitors: Aspirin may reduce the antihypertensive effects of ACE inhibitors. Risk of renal impairment when >300mg/day aspirin is given concomitantly with ACE inhibitors, particularly in patients with poor renal perfusion.

Angiotensin-II receptor antagonists: Concomitant administration with aspirin at doses >3g may reduce the antihypertensive effect of angiotensin-II antagonists. Risk of renal impairment with >300mg/day aspirin, particularly in patients with poor renal perfusion.

Antibacterials: The toxicity of sulfonamides may be increased.

Antidepressants: Increased risk of bleeding when aspirin given with selective serotonin re-uptake inhibitors (SSRIs) or venlafaxine.

Antiemetics: Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

Antiplatelet drugs: Possibility of increased antiplatelet effect, with abnormal bruising and prolonged bleeding time, with clopidogrel or ticlopidine.
Ascorbic Acid: Absorption of ascorbic acid may be reduced.

Calcium channel blockers: Possibility of increased antiplatelet effect, with abnormal bruising and prolonged bleeding time, with calcium channel blockers such as verapamil.

Corticosteroids: The risk of gastrointestinal bleeding and ulceration is increased. Corticosteroids reduce the plasma salicylate concentration~~.~~**,** however, salicylate toxicity may occur when corticosteroids are withdrawn in patients also taking aspirin.

Diuretics: Antagonism of diuretic effect of spironolactone. Reduced excretion of acetazolamide with an increased risk of toxicity. Salicylate intoxication has occurred in patients on high dose salicylate regimens and carbonic anhydrase inhibitors.

Gold compounds: May increase the risk of aspirin-induced liver damage.

Hypoglycaemic agents. Aspirin may enhance the effects of insulin and oral hypoglycaemic agents.

Leukotriene antagonists: The plasma concentration of zafirlukast is increased.

Metamizole may reduce the effect of aspirin on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

Mifepristone: The manufacturer of mifeprisone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

Other non-steroidal anti-inflammatory drugs (NSAIDs): Although plasma concentrations of some other NSAIDs (e.g. indometacin, fenoprofen) may be reduced, concomitant administration of aspirin with other NSAIDs can increase side effects and should therefore be avoided. The combination of low dose aspirin with other NSAIDs should only be used if absolutely necessary and patients on this combination should be closely monitored.

Thyroid function tests: Aspirin may interfere with thyroid function tests.

Uricosurics; Effect of probenecid and sulfinpyrazone reduced. Uricosuric effects of aspirin reduced by phenylbutazone.

Vasodilators: Daily aspirin should not exceed 80mg/day when given with cilostazol.

## 4.6 Fertility, pregnancy and lactation

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Caffeine

Taken during pregnancy, it appears that the half-life of caffeine is prolonged. This is a possible contributing factor in hyperemesis gravidarum. Caffeine crosses the placenta, and foetal blood and tissue levels similar to maternal concentrations are achieved. Cardiac dysrhythmias have been noted in the foetuses and neonates of mothers consuming varying levels of caffeine during pregnancy. Decreased birth weight may be associated with maternal caffeine intake and cigarette smoking. Limited evidence suggests that high maternal caffeine intake may be associated with fetotoxicity including spontaneous abortion, however, other factors may have contributed to the findings. Decreased fertility may be associated with maternal caffeine intake.

Caffeine intake during pregnancy should be kept to a minimum.
Caffeine is excreted in breast milk, but with moderate intake amounts are probably too low to be clinically significant. Regular intake of large amounts of caffeine by nursing mothers can affect the infant including irritability and poor sleeping patterns.

Aspirin

Pregnancy

Low doses (up to and including 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of above 100 mg/day and up to 500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from the epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibition in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%.
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, aspirin should not be given unless clearly necessary.
If aspirin is used by women 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 expose the foetus to:
-cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
-renal dysfunction, which may progress to renal failure with oilgo-droamniosis; the mother and the neonate, at the end of the 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, aspirin at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

From the 20th week of pregnancy onward, Extra Power Pain Control Capletsuse 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, Extra Power Pain Control Caplets should not be given unless clearly necessary. If Extra Power Pain Control Caplets 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 Extra Power Pain Control Caplets for several days from gestational week 20 onward. Extra Power Pain Control Caplets 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, aspirin at doses higher than 100 mg/day is contraindicated during the third trimester of pregnancy (see sections 4.3). Doses up to and including 100 mg/day may only be used under strict obstetric monitoring.

Lactation:
Aspirin should be avoided during breast feeding possible risk of Reye's syndrome

## 4.7 Effects on ability to drive and use machines

**Paracetamol:**
None

**Caffeine:**
None

**Aspirin**:
Aspirin does not usually affect the ability to drive or operate machinery.

## 4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by MedDRA System Organ Class. Adverse reactions identified during post-marketing use are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown but likely to be very rare (<1/10,000).

<u>Post marketing data</u>

Paracetamol

| **Body system** | **Undesirable effect** |
|---|---|
| Blood and lymphatic system disorders | Thrombocytopenia<br>Agranulocytosis |
| Metabolism and nutrition disorders | High anion gap metabolic acidosis (frequency not known) |
| Immune system disorders | Very rare cases of serious skin reactions have been reported.<br>Anaphylaxis<br>Cutaneous hypersensitivity reaction including (amongst others) skin rashes and angioedema |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm – more likely in patients sensitive to aspirin and other NSAIDs |
| Hepatobiliary disorders | Hepatic dysfunction |

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.

Caffeine

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

| **Body system** | **Undesirable effect** |
|---|---|
| Central nervous system | Dizziness<br>Headache |
| Cardiac disorders | Palpitation |
| Psychiatric disorders | Insomnia<br>Restlessness<br>Anxiety and irritability |
| Gastrointestinal disorders | Gastrointestinal disturbances |

Aspirin

Side effects are generally mild and infrequent.

| **Body system** | **Undesirable effect** |
|---|---|
| Blood disorders | Aspirin increases bleeding time, decreases |

| | |
|---|---|
| | platelet adhesiveness and in large doses, may cause hypoprothrombinaemia. It may also cause other blood disorders including thrombocytopenia, aplastic anaemia, agranulocytosis and pancytopenia. Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency |
| Immune system | Aspirin may precipitate bronchospasm and induce dyspnoea, asthma attacks, rhinitis, angioedema, urticaria, rash, or other hypersensitivity reactions in susceptible individuals |
| Gastro-intestinal | There is a relatively high incidence of irritation with nausea, vomiting, diarrhoea and dyspepsia. Slight blood loss, which is often asymptomatic, may occur in some patients; it is not usually of clinical significance but may result in iron-deficiency anaemia during long-term therapy. Haematemesis and/or melaena may occur. It may induce gastrointestinal ulceration and haemorrhage, occasionally major |
| Hepatobiliary | Increased aminotransferase levels, usually reversible on withdrawal; dose-dependent focal hepatic necrosis |
| Renal and urinary disorders | Haematuria may occur |
| Skin | Skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis, may occur in susceptible patients |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below)

Risk Factors.

If the patient

a. Is on long term treatment with carbmazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b. Regularly consumes ethanol in excess of recommended amounts

Or

c. Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdose in the first 24 hours are sweating, pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, hypotension, cerebral oedema, coma and death. Prothrombin time may increase with deteriorating liver function. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrythmias and pancreatitis have been reported.

Treatment

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. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to at least 24 hours post ingestion of paracetamol, however the maximum protective effect is obtained up to eight hours after ingestion. The effectiveness of the antidote decline sharply after this time.

It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

If required the patient should be given intravenous N- acetylcysteine in line with the established dosing schedule. If vomiting is not a problem, oral methionine may be suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations > 350mg/L (2.5mmol/L). Most adult deaths occur in patients whose concentrations exceed 700mg/L (5.1mmol/L). Single doses less than 100mg/kg are unlikely to cause serious poisoning.

Symptoms
Common features include nausea, vomiting, dehydration, headache, tinnitus, vertigo, dizziness, deafness, sweating, warm extremities with bounding pulses, restlessness, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH ( normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arteial pH( raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

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. Cardiovascular collapse and respiratory failure may also occur.

Treatment
Give activated charcoal if an adult presents within one hour of ingestion of more than 250mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis or haemoperfusion are effective methods of removing salicylate from plasma, however, haemodyalisis is the treatment of choice for severe poisoning and should be considered in patients with plasma-salicylate concentrations mg/litre (5.1mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine
Symptoms: Large doses may cause restlessness, excitement, psychosis, muscle tremor, tinnitus, hyperglycaemia, hypokalaemia, diuresis, dehydration, tachycardia and extrasystoles. Emesis and convulsions may occur.

Treatment
No specific antidote. Elimination may be enhanced by repeated oral doses of activated charcoal. Symptomatic and supportive treatment.

Hypokalemia should be corrected by intravenous infusion of potassium chloride.

Intravenous diazepam or barbiturates may be used to control convulsions.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Paracetamol
Paracetamol has analgesic and antipyretic properties. Analgesic effects are thought to be related to inhibition of prostaglandin synthesis. An antipyretic effect has been demonstrated where fever exists but normal body temperature is not lowered. The drug acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow. The failure of paracetamol to exert anti-inflammatory activity may be attributed to the fact that it is only a weak inhibitor of cyclo-oxygenase in the presence of the high concentrations of peroxides that are found in inflammatory lesions. Further, paracetamol does not inhibit neutrophil activation as do other NSAIDs.

Single or repeated therapeutic doses of paracetamol have no effect on the cardiovascular and respiratory systems, nor does the drug produce gastric irritation, erosion, or bleeding.

Aspirin
Aspirin is a non-steroidal anti-inflammatory agent that acts by inhibition of prostaglandin synthetase.

Caffeine
The primary effect of caffeine is central nervous system stimulation, mainly on the higher centres. This expressed in terms of increased vigilance, wakefulness, relief from fatigue, increased mental activity, improved performance and improved mood. Other effects include diuresis and increased cardiac output with peripheral vasodilation. Caffeine, a methylxanthine, exerts its pharmacological effects by increasing calcium permeability in the sarcoplasmic reticulum, inhibiting phosphodiesterase and promoting accumulation of cyclic AMP. Caffeine is also a competitive, non-selective antagonist at adenosine A1 and A2A receptors. Evidence suggests that adenosine receptor antagonism is the most important factor responsible for most pharmacological effects of methylxanthines in doses that are administered therapeutically.

## 5.2 Pharmacokinetic properties

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract, with peak plasma concentrations reached in 10-15 minutes after oral dosing. Dissolution and gastric emptying are rate-limiting steps; the mean half-time of absorption from upper small intestine is within minutes. The absolute oral bioavailability is about 80% and is independent of dose in the range 5 to 20 mg/kg. Oral bioavailability of paracetamol is subject to first pass metabolism. Paracetamol is rapidly and uniformly distributed into most body tissues. About 25% of paracetamol in blood is bound to plasma proteins. The mean plasma paracetamol half-life following a therapeutic dose is about 2.3 hours in healthy adults, with a range of 1.5 - 3 hours. Paracetamol crosses the placenta and is present in breast milk.

After therapeutic doses, 90-100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%) or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites have also been detected. A small proportion of paracetamol undergoes P450-mediated N-hydroxylation to form N-acetyl-benzoquinoneimine, a highly reactive intermediate. After large doses of paracetamol, this metabolite is formed in amounts sufficient to deplete hepatic glutathione. Under these circumstances, reaction with sulfydryl groups in hepatic proteins is increased and hepatic necrosis can result. Renal clearance is about 10 ml/min.

Aspirin

Aspirin is rapidly absorbed after oral administration, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks. Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates (ion-exchange resins) and antacids.

Peak plasma concentrations of approximately 45 mg/l are attained 1 to 2 hours after an oral dose of 640 mg aspirin, but stabilise at approximately 270 mg/l after oral doses of 3 g daily.

The plasma aspirin half-life is approximately 17 minutes; the plasma salicylate half-life is approximately 2-4 hours in low doses but up to 19 hours with high doses.

Aspirin is found in the saliva, milk, plasma and synovial fluid at concentrations less than blood and crosses the placenta. Salicylate demonstrates extensive protein binding; aspirin binds to a lesser extent.

Aspirin undergoes rapid hydrolysis in the blood to salicylic acid. Glucuronic acid/glycine conjugation leads to formation of glucuronides and salicyluric acid; a small proportion undergoes oxidation.

Aspirin is excreted in urine mainly as salicylphenylglucuronide and salicyluric acid. Free salicylate is reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of a dose is excreted as free salicylate.

Caffeine

Caffeine is absorbed readily after oral administration to the extent of 99%, peak plasma levels occur in 15-45 min. The half-life of caffeine in plasma shows considerable variation with the reported values ranging from 3.0-7.5 hours. It is widely and rapidly distributed throughout the body, and passes readily into the central nervous system and saliva. Approximately 17% of the drug is bound to plasma proteins. Caffeine crosses the placenta and has been shown to distribute into milk in a milk-to-serum concentration of 0.52.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine and other metabolites with only about 1% unchanged. Neonates have a greatly reduced capacity to metabolise caffeine and it is largely excreted unchanged in the urine until hepatic metabolism becomes significantly developed.

### 5.3 Preclinical safety data

The active ingredients have been in widespread use for many years and have a well established therapeutic profile. There is no further data of relevance to the prescriber in addition to that presented in the other sections of the SmPC.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Povidone
Hydroxypropylcellulose
Stearic Acid
Microcrystalline cellulose
Maize starch
Pregelatinised starch

Coating contains:
Hydroxypropyl methylcellulose 5 cPs
Hydroxypropyl methylcellulose 15 cPs
Macrogol 4000

### 6.2 Incompatibilities

None.

### 6.3 Shelf life

2 years from the date of manufacture

### 6.4 Special precautions for storage

Do not store above 25°C

### 6.5 Nature and contents of container

Tablets are packaged in blisters.

Blister strips consist of a 35gsm paper/9µ soft tempered aluminium foil lid and 250µ PVC/PVDC film base in cartons.

Pack sizes: 28, 32 (P)

### 6.6 Special precautions for disposal

No special instructions

## 7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
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