Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Panadeine Extra Strength Tablets Paracetamol 500 mg Codeine Phosphate hemihydrate 12.8 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol Ph Eur 500 mg and Codeine Phosphate Hemihydrate Ph Eur 12.8 mg.
Excipient: Contains 5.9 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet
Red, film-coated, capsule-shaped tablets. Embossed on one side with "Extra".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Panadeine Extra Strength Tablets is indicated in patients 12 years and older for the treatment of acute moderate pain (rheumatic pain, headaches, backache, musculoskeletal pain, migraine, toothache, sore throat, period pains, feverishness and the symptoms of colds and influenza) which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

4.2 Posology and method of administration

For oral use only.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Adults and children aged 16 years and over:

One to two tablets to be taken with water three to four times daily as required.

Paediatric population
Children aged 12-15 years:

One tablet to be taken with water three to four times daily as required.

Panadeine Extra Strength is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough or cold (see section 4.4).

Panadeine Extra Strength Tablets should be used at the lowest effective dose for the shortest period of time. The dose should not be repeated more frequently than every six hours, and not more than four doses should be given in any 24-hour period.

Children aged less than 12 years:

Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Panadeine Extra Strength is contraindicated in children below the age of 12 years for the symptomatic treatment of cough or cold (see section 4.3)

Renal impairment:

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:
Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:
In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. The daily dose should not exceed 2g/day unless directed by a physician.

The elderly:
Experience has indicated that normal adult dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate. The maximum daily dose should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:
- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

4.3 Contraindications

History of hypersensitivity to paracetamol or codeine or to any of the excipients. Acute asthma.
Use of codeine containing products is contraindicated in women during breastfeeding (see section 4.6).

Codeine is contraindicated in all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life- threatening adverse reactions (see section 4.4).

Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough or cold due to an increased risk of developing serious and life-threatening adverse reactions.

Codeine is contraindicated in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

CONTAINS PARACETAMOL and CODEINE. Do not take with other paracetamol or codeine-containing products. Do not exceed the stated dose.

Do not take for more than three days unless told to do so by your doctor.

Prolonged or frequent use is discouraged. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration

- Chronic malnutrition
- Weight less than 50kg
- Elderly

The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Care should be observed in administering the product to any patients whose condition may be exacerbated by opioids, particularly the elderly, who are especially sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostate hypertrophy and those with inflammatory or obstructive bowel disorders.
Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped.

CYP2D6 metabolism
Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra- rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.
Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29
African American	3.4 to 6.5
Asian	1.2 to 2
Caucasian	3.6 to 6.5
Greek	6.0
Hungarian	1.9
Northern European	1 to 2

Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine."

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Panadeine Extra Tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Panadeine Extra Tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patient should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Prolonged use without medical supervision can be harmful. If high fever or signs of secondary infection occur of if symptoms persist, consult your doctor.

In cases of renal insufficiency, the rate of excretion of codeine and paracetamol metabolites may be reduced and dosage schedules may need to be revised accordingly.

Keep out of the sight and reach of children.

This product should only be used if clearly necessary.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Opioid analgesics should be given with care to patients receiving monoamine oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of the additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Panadeine Extra Strength Tablets should not be used during pregnancy.

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.

There are no adequate data from the use of codeine in pregnant women.
Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Lactation
Panadeine Extra Strength Tablets are contraindicated in women during breastfeeding (see section 4.3). At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result
in symptoms of opioid toxicity in the infant, which may be fatal.

Paracetamol is excreted in breast milk but not in a clinically significant amount.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by drowsiness.

4.8 Undesirable effects

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been very rare reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily causally related to paracetamol.

Codeine may cause constipation, nausea, dizziness and drowsiness according to dosage and individual susceptibility.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Immediate medical attention (in hospital, if possible) is required in the event of overdose, even if there are no significant early symptoms. There may be no early symptoms following a life-threatening overdose. Ingestion of more than 12 g paracetamol (24 standard 500 mg tablets) or more than 150 mg paracetamol per kg bodyweight (9 g paracetamol in a 60 kg individual), whichever is the smaller, can cause severe liver damage. Liver damage (as demonstrated by a rise in plasma transaminase levels) may be apparent between 8 and 36 hours following overdose. Biochemical evidence of maximal damage, however, may not be attained until 72-96 hours after ingestion of the overdose.

Intravenous N-acetylcysteine (NAC) is effective when initiated within eight hours of the overdose. Efficacy declines progressively after this time, but NAC may provide some benefit up to and possibly beyond 24 hours.
Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose. Activated charcoal should be considered if the dose of paracetamol ingested exceeds 12 g or 150 mg/kg, whichever is the smaller, and the procedure can be undertaken within one hour of the overdose. There is little evidence that undertaking gastric lavage will be of benefit to a patient in whom paracetamol is known to have been the only substance ingested.

Symptoms of paracetamol overdose in the first 24 hours may include pallor, nausea, vomiting, anorexia, and abdominal pain. Abnormalities of glucose metabolism, and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Liver damage results when excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Nausea and vomiting are prominent symptoms of codeine toxicity and there is evidence of circulatory and respiratory depression. Suggested treatment is gastric lavage and catharsis, e.g. sodium sulphate 30g. If CNS depression is severe, assisted ventilation, oxygen and parenteral naloxone may be needed.

Overuse of this product (either by taking for more than three days and / or taking a higher than recommended dose) may lead to physical or psychological dependency, including withdrawal symptoms such as restlessness and irritability on abrupt discontinuation of treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: N02AJ06 – Codeine combinations excluding psycholeptics.

Paracetamol is an analgesic and antipyretic.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through mu opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Concentration of paracetamol in plasma reaches a peak in 30-60 minutes. The plasma half-life of paracetamol is one to four hours. Paracetamol is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost exclusively renal, in the form of conjugated metabolites.

Codeine phosphate is well absorbed after oral administration and is widely distributed. Peak plasma concentrations occur between 30 minutes and two hours after ingestion. The plasma half-life varies between three and four hours. About 85% of an oral dose is excreted in the urine within 24 hours, 40 to70% is free or conjugated codeine, 5 to15% is free or conjugated morphine, 10 to 20% is free or conjugated norcodeine, and trace amounts may be free or conjugated normorphine.

Concurrent administration of paracetamol and codeine does not interfere with the normal metabolic processes of each agent.

5.3 Preclinical safety data

Studies in animals have revealed no adverse effects on reproduction, and no teratogenic effects of paracetamol at doses well in excess of the human therapeutic dose. Paracetamol is not associated with a genotoxic or carcinogenic risk.
Conventional studies using the currently accepted standard for the evaluation of paracetamol toxicity to reproduction and development are not available.

Studies in rats and mice have revealed no abnormal development or embryolethal effects of codeine at doses of 10- 20 mg/kg and 5-30 mg/kg respectively. Codeine showed no genotoxic activity in the Ames test, mouse and rat micronucleus assays, and only induced chromosome aberrations in Chinese Hamster Ovary (CHO) cells at concentrations that delayed the cell cycle.
There was no evidence of carcinogenic activity of codeine in mice and rats fed up to 3,000 and 1,600 ppm codeine, respectively, for two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Pregelatinised starch
Potassium sorbate
Povidone
Talc
Magnesium Stearate
Microcrystalline cellulose
Stearic acid
Croscarmellose sodium
Lactose Monohydrate
Hypromellose (E464)
Macrogol 4000
Quinoline Yellow (E104)
Erythrosine (E127)
Titanium Dioxide (E171)

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

PVC/aluminium foil blister in cardboard cartons, containing 4, 6, 10, 12, 16, 20, 24, 32, 48, 60 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/026/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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