Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Panadeine Tablets.
Paracetamol 500mg
Codeine Phosphate Hemihydrate 8mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500 mg and codeine phosphate hemihydrate 8 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, flat, circular bevel-edged tablets marked with the word ‘Panadeine’ on one surface and a single scoreline on the other.
The scoreline allows the tablet to be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Panadeine Tablets is indicated in patients 12 years and older for the treatment of acute moderate pain (headache, toothache, dysmenorrhoea and musculosketal pain) that cannot be considered relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Oral administration only.

Adults (including the elderly) and children aged 12 years and over:

1-2 tablets to be taken with water three to four times daily as required.

Panadeine Tablets should be used at the lowest effective dose for the shortest period of time. Doses should not be repeated more frequently than every six hours and not more than 4 doses (8 tablets) should be given in any 24 hour period.

Do not exceed the stated dose.
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.

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).

4.3 Contraindications

History of hypersensitivity to paracetamol, codeine or any of the other constituents.

Acute asthma.

Use of codeine containing products is contraindicated in mothers who are breast feeding (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 those patients who are known to be CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

Care is advised in the administration of paracetamol to patients with severe renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the stated dose.

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

Prolonged use except under medical supervision can be harmful. If symptoms persist, or worsen, medical advice must be sought.

This product should only be used if clearly necessary.

Patients should be advised not to take other paracetamol or codeine containing products concurrently.

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.

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’ should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

<u>CYP2D6 metabolism</u>
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.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

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

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

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.

Codeine

Codeine may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility.

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOI) and result in serotonin syndrome.

The effect of CNS depressants (including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressant and phenothiazine) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate.

The safety of paracetamol-codeine during pregnancy has not been established relative to the possible adverse effects on foetal development.

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

Codeine-containing products must not be used while 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.

4.7 Effects on ability to drive and use machines

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

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 System Organ Class and frequency.

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data and are considered to be very rare.

Paracetamol

Body System	**Undesirable Effect**
Blood and lymphatic system disorders	Thrombocytopaenia
Immune System disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema, and Stevens Johnson syndrome
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAID’s
Hepatobiliary disorders	Hepatic dysfunction

Codeine
Adverse reactions identified during post-marketing use are listed below by MedDRA System Organ Class. The frequency of these reactions is not known.

Body System	Undesirable Effect
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine at higher doses
Gastrointestinal disorder	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy
Nervous system disorder	Dizziness, worsening of headache with prolonged use, drowsiness
Skin and subcutaneous tissue	Pruritus, sweating

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

Paracetamol

Symptoms and signs
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.

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.

Treatment
Immediate medical attention (in-hospital, if possible) is required in the event of overdose, even if there are no significant early symptoms.

Intravenous N-acetylcysteine (NAC) is effective when initiated within 8 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 1 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.

Codeine

Symptoms and signs
An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

Treatment
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg of codeine or a child more than 5 mg/kg of codeine. Give naloxone if coma or respiratory depression is present. Observe for at least four hours after ingestion or eight hours for a sustained release formulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code/pharmacotherapeutic group: N02AJ06

Paracetamol is an analgesic and antipyretic.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ 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 completely absorbed from the gastro-intestinal tract. Concentration in plasma reaches a peak in 30 – 60 minutes. Plasma half-life is 1 – 4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids. Plasma protein binding is variable.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86% is excreted in the urine in 24 hours; 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine and 10-20% is free or conjugated norcodeine.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Povidone
Potassium sorbate
Microcrystalline cellulose
Stearic acid
Magnesium stearate
Talc
Pregelatinised starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

PVC blisters in packs of 12, 24 or 48 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0678/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 29th March 2008

10 DATE OF REVISION OF THE TEXT

July 2015